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THE DIAGNOSIS OF PARAPHYSIAL CYSTS

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PARAPHYSIAL cysts, more commonly known as colloid cysts of the 3rd ventricle, are histologically benign intracerebral tumours the importance of which has been increasingly recognized in recent years. Despite their small size—they rarely exceed 2 to 3 cm. in diameter—and their completely benign cellular character, they are, by virtue of their position, a menace to life. In the majority of reported cases the diagnosis has been made only at autopsy. In the last fifteen years, however, the number of cases diagnosed in life and, in many cases, successfully operated upon has rapidly grown.

A confident diagnosis by clinical methods is extremely difficult, and in many cases would appear impossible. A highly suggestive clinical history and pattern may exist, but atypical cases with puzzling or misleading symptomatology are common, and diagnosis, on clinical grounds, though often suspected, is rarely made with any degree of sureness. Therefore, the possibility of accurate diagnosis depends primarily on ventriculography. It is the purpose of this paper to show that ventriculography, when conducted with a careful technique, will enable the diagnosis of paraphysial cyst to be made with certainty in almost every case.

That this is not yet fully realized, even among neurosurgeons, is demonstrated on P. 354 of " Intracranial Tumours " by P. Bailey (2nd Edition, 1948), where it is stated that " there is no way of making a positive diagnosis of such a tumour."

It is hoped that this paper will help to prove that this is no longer a justifiable opinion.

LITERATURE

The first reported case in the literature appears to be by Wallman in 1858. There were still less than 50 recorded cases when Dandy (1933) published his classic monograph. His series of 5 cases was the largest

published till then, and he reported the first successful operative removal of a colloid cyst. The operation was performed in 1921.

Since then the number of operated cases has rapidly grown and is increasing. Grossiord (1941) exhaustively reviewed the whole literature prior to 1938 and listed 79 cases, to which he added 2 more, making a total of 81 recorded cases at that date. Of these no less than 25 had had their cysts diagnosed and operated on. There were 22 cures and 3 deaths, an impressive indication of the alteration in prognosis. 5 cases were misdiagnosed and died after palliative or other operation.

Adding cases published since Grossiord's exhaustive survey, the total of recorded cases is now at least 110.[1] 37 of these are reported as operatively cured, and 12 as dying after operative intervention either for the cyst or for a wrongly suspected posterior fossa or otherwise localized lesion. Almost all operated cases underwent ventriculography, and a few encephalography. We consider the former method of air study the method of choice, and the latter contra-indicated in this type of case, which usually provides evidence of raised intracranial pressure.

Material

In this paper 24 cases are discussed. 22 underwent ventriculography and the ventriculographic findings in the 20 of these available have been analysed by us. Only two of the cases have been previously reported (Case 2 by Jefferson 1937, and Case 3 by Jefferson and Jackson, 1939). A total of 22 cases is therefore added to the literature, of which 20 underwent ventriculography. A correct diagnosis of paraphysial cyst or 3rd ventricle tumour was eventually made in 19 of these cases. One of the early cases (No. 6) was misinterpreted as a posterior fossa lesion, but review of the films shows that the diagnosis was in fact possible from the air studies. The 19 diagnosed cases were operated on with cure of 15, and death followed operation in 4.

Of the 12 cases which were examined by us personally a positive diagnosis of paraphysial cyst was made in 11, and the other was diagnosed as a 3rd ventricle tumour.[2]

Æetiology

The cysts are now generally believed to be of embryonic origin, being derived from the paraphysis. This is a glandular structure found in some lower vertebrates, arising just behind the foramina of Monro as an

[1]Traut and Piette, 1938; Lindon, 1938; Campbell and Schwind, 1939; Neustadter and Meltzer, 1939; Jefferson and Jackson, 1939; Niven, 1939; Shaver, 1940; Campbell and Whitfield, 1940; Zeitlin and Lichtenstein, 1940; Larson, 1940; Madeheim, 1941; Ectors, 1942; Weinberger and Boshes, 1943; Shannon, 1944; Moss, 1945; Massachusett's General Hospital case report, 1946; Ward and Spurling, 1948; Pennybacker and Russell, 1948; Lysholm, 1948; Torkildsen, 1948.

[2]See postscript.

evagination in the mid-line from the roof of the 3rd ventricle. A rudimentary paraphysis occurs as a transient structure in the human embryo whilst it is between 19 and 32 mm. in length. A persistence of this vestigial structure gives rise to colloid cysts, which are therefore more accurately termed paraphysial cysts (Bailey, 1916; McLean, 1936; Krabbe, 1936).

Other theories are that the cysts are of choroidal or ependymal origin.

Pathological Anatomy

The cyst lies in the mid-line in the roof of the 3rd ventricle and directly behind the foramina of Monro. As it grows it projects downwards into the 3rd ventricle, and to a varying extent upwards and forwards. It is therefore in intimate relationship with the choroid plexus, and, being at first mobile, can obviously give rise to intermittent blockage of the foramina of Monro (figs. 1A and 1B—*facing page* 516).

Small and clinically unimportant paraphysial cysts have been observed as incidental findings at autopsy (Krabbe, 1936). The usual size of those causing symptoms and seen at operation or autopsy is 1 to 2 cm. in diameter (figs. 2A and 2B), though larger cysts are often reported. One, described by Zeitlin and Lichtenstein (1937), measured 5 cm. × 3·5 cm.

Rupture of the cyst into the brain tissue has been described by Larson (1940) in an apparently unique case. It is interesting that this occurred in the oldest person (aged 72) in whom a cyst has yet been reported.

The cyst has a thin semitransparent wall and is usually greenish or blue-green in colour. As a rule it has a homogeneous colloid content, the colour of which seems to vary considerably, and has been described in different reports as "greenish," "yellowish," "greyish," etc. The consistency also varies and is commonly viscid or sticky, and sometimes too tenacious for aspiration. A few authors describe the contents as "dirty" or "cheesy" material resembling that found in epidermoid cysts. Cholesterin crystals may be present, a point which we will return to later.

Grossiord discussing the histology is of the opinion that the typical lining is unicellular, and that the appearance of several layers is often an artefact due to oblique sectioning. However, there is no doubt that the lining may often be several cell layers thick, though careful search will usually reveal the characteristic unicellular ciliated lining at some point. Again, an appearance suggesting a cystic papilloma is occasionally seen, due to infolding or to projecting papillæ. Sometimes the epithelium may even be described as "squamous" in parts, in apparently otherwise typical paraphysial cysts.

It is not surprising, therefore, that in some cases these cysts have been described as dermoid or epidermoid cysts. Grossiord has listed 7 such cases, and points out that histologically none of them is really typical of an epidermoid, and in most the epithelial lining is that of a paraphysial cyst. A similar case was presented by Jefferson and Jackson (1939) as

a dermoid cyst. The histological section shown seems more typical of a paraphysial cyst, and shows no evidence of squamous epithelium. To quote Love and Kernohan (1936):

"We consider squamous epithelium that can be identified as such a necessary criterion for the microscopic diagnosis of an epidermoid tumour. We have studied several tumours the contents of which were typical of dermoid or epidermoid tumours, but when we could not identify squamous epithelium in the walls of these cysts, we did not classify them as dermoids or epidermoids."

One case of this type has been encountered in our material, and a second was brought to our notice by Mr. J. E. A. O'Connell who has kindly allowed us to publish details (Cases 11 and 21 respectively).

Dr. H. Dimsdale who originally reported on Case 11 as a "squamous epitheliomatous cyst," has reviewed the sections and now states there is no doubt that the tumour is a paraphysial cyst.

Mr. O'Connell thought at operation that his case was a dermoid but histopathology showed that it too was a paraphysial cyst (Case 21).

Grossiord sums up the position with regard to paraphysial cysts resembling dermoids as follows. He refers in particular to the occasional presence of cholesterin.

"cette presence de cholesterine n'a rien en fait de très particulier, elle indique seulement la présence d'un certain pouvoir epidermique; l'origine embryologique de l'ependyme, l'inclusion embryonnaire qui est la base de ce kyste, son developpement kystique remplissent pleinement de telles conditions. Tout se reduit au fond à une question de mots; les limites precises du "kyste colloide" sont bien difficiles à préciser et nous pensons qu'il existe des formes de transition entre les kystes a bordure cylindrocubique ciliée et ceux qui ont un epithelium squameux et qui font de la cholesterine."

It seems to us that these "dermoids" show little difference clinically, radiologically or histologically from true paraphysial cysts and that their treatment should be the same.

Clinical Aspects

Sex.—There is no marked predilection for either sex. In 100 cases traced in the literature there were 55 males and 45 females. Of our 22 unreported cases 16 were male and 6 female, giving a total of 71 males and 51 females out of 122 cases.

Age.—The cysts usually present in adults between the ages of 20 and 50. The youngest case reported was aged 11 years at diagnosis (Dandy, 1933), the oldest 72 (Larson, 1940). An analysis of the age incidence in 118 cases (including our own) gives the following figures:

Below 20 — 10 cases (youngest 11 years)
20–30 — 34 cases
30–40 — 33 cases
40–50 — 30 cases
50–60 — 9 cases
60 and over 2 cases (oldest 72 years)

Symptoms and signs.—Clinically no sign is characteristic. The most suggestive feature is a succession of intermittent crises. These may be of various types from headaches with or without vomiting to more or less prolonged coma. Paroxysms of headache are usually of sudden acute onset with periods of remission. In some cases the attacks may be affected by posture, a suspicious though infrequent sign. They are considered to be due to acute hydrocephalus caused by the cyst blocking the foramina of Monro. Obstruction of the veins of Galen may also play a part. Papillœdema is usually present.

Infundibulo-endocrine symptoms may occur, and confuse the issue. Cerebellar signs may lead to a posterior fossa lesion being suspected. Mild pyramidal signs are not infrequent, as are ocular palsies. The pupils may be small and their reactions poor. Visual field defects may even occur (Case 13). Attacks in which the patient momentarily loses the power of his legs and falls, but is not unconscious (as in Case 18), have been reported in several cases. Again cases may present with psychic disorders (Riddoch, 1936) or remain silent completely.

The duration of symptoms is often dubious. Most cases have a history of less than twelve months between onset and diagnosis or death. Some, however, had symptoms for many years.

The eventual prognosis is always bad, and all cases are liable to sudden death in an attack of acute hydrocephalus (Case 17).

Surgical extirpation is the only treatment and successful results are dramatic. Deep X-ray treatment is useless, though Ward and Spurling (1948) recommend X-ray therapy in cases of third ventricle tumour where the diagnosis remains in doubt, with exploration later if there is no improvement in the patient's condition. We hope to demonstrate that a positive diagnosis should nearly always follow ventriculography in cases of paraphysial cyst, and in those few cases where it does not we would advise exploration.

An interesting case, in which failure to recognize the lesion was followed by X-ray therapy for a supposed malignant condition, is reported by Pennybacker and Russell (1948). In this case autopsy showed severe brain necrosis as a result of the treatment.

Radiological Aspects

Plain X-ray.—The plain X-ray findings are not of very great assistance. The films of 20 cases were examined or reviewed by us. They were considered as within normal limits in 10 (Cases 2, 4, 8, 10, 11, 12, 14, 20, 21, and 24), and as showing evidence of raised intracranial pressure with no localizing signs—as one would expect—in the other 10. The evidence in all these latter cases (Nos. 6, 7, 9, 13, 15, 16, 18, 19, 22 and 23) consisted only of sellar changes. There was thinning or erosion of the dorsum sellæ in all, and slight sellar enlargement of the type associated with generally raised intracranial pressure in two (Cases 11 and 12).

Displacement of the calcified pineal downwards is a plain X-ray finding reported in a few cases (Davidoff and Dyke, 1935 ; Jefferson and Jackson, 1939). The pineal was calcified in only 6 of our cases, and in none of these was it considered displaced.

Pneumo-encephalography.—Ventriculography is the method of choice. Encephalography, as has already been stated, is regarded by us as dangerous in this type of case, in which clinical evidence of raised intracranial pressure is usually present. (Papillœdema was in fact present in 22 out of the 24 cases discussed in this paper.)

The diagnosis of the lesion rests essentially on the ventriculographic picture. Not only is the localization of the tumour given, but its size, shape, cystic quality and pathological nature are also revealed. There are very few intracranial expanding processes of which so much can be learnt from air pictures. With the majority of intracranial tumours we may be satisfied if the position and size can be predicted. Since parapysial cysts are benign lesions it is obvious that a great responsibility rests on the radiologist in making a correct interpretation. We are convinced that this is possible in nearly every case, and that in the small proportion of cases where exact diagnosis is not possible, the possible presence of this tumour must be borne in mind.

From a study of the literature we feel that the pathognomonic radiological signs have not been sufficiently stressed or sufficiently carefully sought in the past. Grossiord in his very complete survey has analysed all the pneumographic findings prior to his paper, and reported a satisfactory diagnosis in only a little more than half of the ventriculograms examined (16 out of 28 cases). Even Lysholm (1948) only claims that 11 out of the 16 cases occurring in his material were characteristic.

In our material consisting of 20 cases, the ventriculograms of which have been analysed, the pathognomonic signs enabling a confident diagnosis to be made have been present in 19 (all except Case 16).

Tracings of the relevant portion of the ventricular system in each case are shown below, and the X-ray findings discussed.

Technique and findings.—Our ventriculographic routine is as follows : Three preliminary radiographs are taken in the supine position (anteroposterior, half-axial, and horizontal ray lateral), following Lysholm's technique. Air injection may have been carried out by tapping one or both ventricles. For reasons which are apparent below, we believe that the latter method is preferable in these cases. The possible findings are various and may be analysed as follows :

A. When ventriculography is carried out by tapping only one ventricle the following pictures may result.

(1) The foramina of Monro may be completely occluded and a single dilated ventricle will be shown, lying towards the mid-line. This is due to the relatively increased pressure in the air-filled ventricle which causes the septum pellucidum to balloon across the mid-line. (As in Case 16 on first ventriculogram.)

(2) If the homolateral foramen of Monro is not completely blocked some air may enter the 3rd ventricle and the picture above described may be associated with a partially filled non-dilated 3rd ventricle in which the cyst is outlined. (As in Cases 13 and 19.)

(3) The septum pellucidum may have ruptured, and despite the blocked foramina of Monro symmetrically dilated lateral ventricles will be shown with a vertical and central septum pellucidum. Dandy (1933) claims that the rupture may actually be visualized.

(4) The foramina of Monro may be patent and thus allow both lateral ventricles and the 3rd ventricle to fill and so outline the tumour (as in Cases 7, 10 and 11). (This possibly occurred in Cases 14 and in the original ventriculogram of Case 18.)

B. If ventriculography is carried out by tapping both ventricles the following appearances may result.

(1) Symmetrically dilated lateral ventricles with non-filling of the 3rd ventricle, the foramina of Monro being completely blocked. In this case the septum pellucidum may be bulged to one side by unequal pressure in the two ventricles (unless, of course, a rupture allows equalization).

In such cases the following pictures may be seen :

(*a*) Despite non-filling of the 3rd ventricle the cyst may still be partially visualized, its upper rounded margin bulging into the inferomedial margins of the lateral ventricles in the antero-posterior brow-up position. In addition the half-axial brow-up position may reveal its shadow, or the lateral view show its rounded upper margin. (As in Cases 12, 21 and 22 and in the second ventriculogram of Case 18.)

(*b*) The cyst may not be shown at all. This occurred in only one case, and in our opinion should very rarely happen if a careful technique is used. (As in Case 16 at second ventriculogram and myodil ventriculogram.)

(2) Symmetrical hydrocephalus with partial filling of a non-dilated 3rd ventricle. In this case the tumour is outlined, as in many of our cases. (As in Cases 2, 4, 6, 8, 9, 15, 19, 20, 23 and 24.)

The 3rd ventricle in many cases was not immediately visualized. It is this group of cases which requires further radiological investigation, and perseverance with manipulation of the head will nearly always give the diagnosis. From a study of the literature we are convinced that this procedure has not been sufficiently used. In our personal experience of 12 cases we have failed only once. The manipulative procedure consists in taking hold of the head, with the patient in the supine position and gently extending it until the plane of the base-line is roughly horizontal. The head is then gently shaken and the patient asked to listen for bubbles. If he hears them one is fairly safe in assuming that air has passed either from one lateral ventricle to the other or into the 3rd ventricle. Even if bubbles are not heard the air may still have flowed into the required position. Following this procedure the head is maintained in the same position and a lateral radiograph taken with a horizontal ray. If the film fails to show the 3rd ventricle the manipulation

is repeated. We believe that with this technique there should be only occasional failure to manipulate some air into the 3rd ventricle and outline the tumour.

The cyst is best seen, we find, in the following three views:

(1) The lateral view (fig. 3), especially the "hanging head" lateral just described.

(2) The half-axial view with the brow up, where the tumour is seen as an ovoid defect at the lower part of the septum pellucidum (fig. 4).

(3) The antero-posterior view with brow up, where the cyst shows as a semicircular defect at the lower end of the septum pellucidum, as emphasized by Twining (1939) (fig. 5).

Special attention is paid to these three projections once the nature of the lesion is suspected, and they are very carefully examined—for the shadow of the cyst may be very faint, especially if the 3rd ventricle has failed to fill. It should be noted that even with non-filling of the 3rd ventricle the tumour may still be seen in the half-axial or brow-up antero-posterior view (*see* figs. 4 and 5).

An important point here is that air filling must be adequate to reach behind the foramina of Monro in the brow-up position and outline the upper part of the tumour. Otherwise the outline of the tumour in views (2) and (3) just mentioned will not be shown. This happened in Case 20 and though we were quite confident of the diagnosis on visualizing the tumour in the "hanging head" lateral view, we had the greatest difficulty in convincing the neurosurgeon of this as he considered the evidence inadequate.

Even in such a case it may still be possible to obtain adequate antero-posterior and half-axial films by taking them with the head as near as

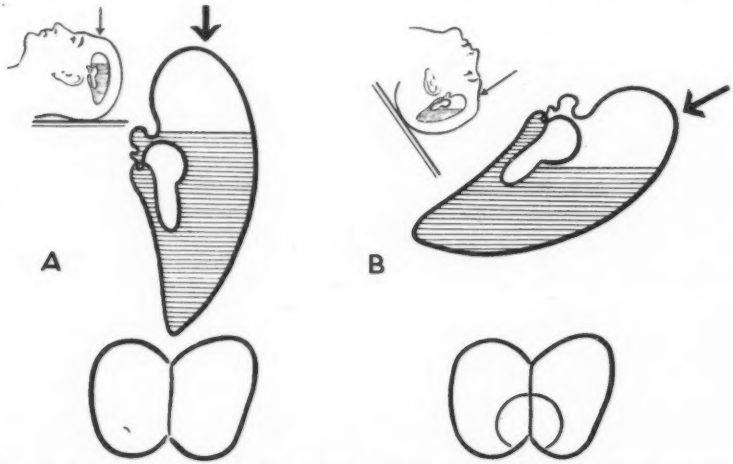

FIG. 6.—To illustrate the value of the "hanging head" antero-posterior projection when air filling is inadequate.

possible in the " hanging head " position of view (1). The small amount of air present is thus brought into contact with the cyst, which would otherwise be covered by fluid (fig. 6). Though we have obtained diagnostic pictures by this means in cases with poor air filling (Case 24) it should be emphasized that good filling of the ventricular system should always be aimed at to ensure good results. Refinements of technique, however helpful, should not be regarded as a substitute for unsatisfactory filling and the surgeon should be urged to inject more air, if this is at all possible when the amount already present appears inadequate.

These three projections (figs. 3, 4 and 5) or such of them as are available have been traced in all the ventriculograms examined and it is clearly demonstrated that the shadow of the tumour can almost invariably be recognized.

Fig. 7 is a generalized lateral view of the ventricles based on this series,

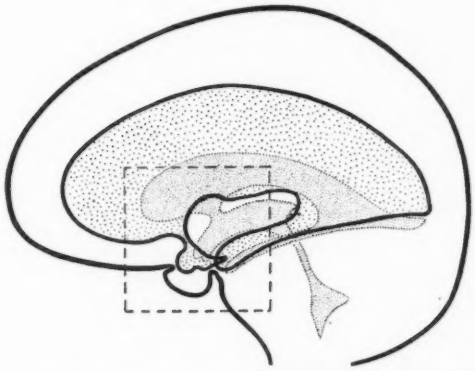

FIG. 7.—The ventricular system as seen in a case of paraphysial cyst is shown in coarse stippling is superimposed upon a normal ventricular system (after Lysholm) in fine stippling. Owing to the smallness of the figure, the relations of the two are best seen if a reading glass is used. The inset area is traced in the case reports.

with a normal ventricular system (after Lysholm) superimposed. The inset area has been traced in the series of diagrams below. The figure illustrates clearly an important point of differential diagnosis ; that the foramen of Monro, when visualized, is seen to be anterior to its normal position (in some cases strikingly so), and to be narrowed. As far as we are aware this observation has not previously been described.

We would draw attention to another point not previously emphasized in ventriculography of these cases, the presence of septum pellucidum cysts in Cases 8, 14 and 15, and the suspicion of their presence in other cases.

This suggests an unduly high incidence of the anomaly in cases of paraphysial cyst. We can find only two references in the literature

(Neustadter and Meltzer, 1939; Larson, 1940) but this is a lesion likely to be missed except by those especially interested in it.

Positive contrast ventriculography.—In only one case (No. 16) did both the third and opposite lateral ventricles fail to fill with air even after much manipulation of the head. Myodil was introduced into the lateral ventricle in this case. We hoped that it would pass through the foramen of Monro, but it failed to do so. Myodil was used by us in only one other case (No. 19); again only one lateral ventricle had been filled with air by the surgeon and manipulation had failed to transfer any air to the other lateral ventricle. However, a little air had entered the anterior part of the 3rd ventricle. A typical filling defect was seen here, immediately behind the foramen of Monro. This sign, combined with an absence of dilatation of the anterior end of the 3rd ventricle, and the patient's history, made us strongly suspect that a paraphysial cyst was present, but we were anxious to clinch the diagnosis by demonstrating myodil outlining the edge of the cyst.

Two cubic centimetres of myodil were introduced into the lateral ventricle, but none passed the foramen in spite of repeated manipulations under the fluorescent screen.

The lessons to be learnt were that (*a*) myodil will not always pass a partial block which air will pass, and (*b*) if air fails to pass, myodil will certainly also fail on account of its greater viscosity.

Myodil was also used by a colleague in Case 22 with results which confirm the above findings and conclusions.

Arteriography.—Percutaneous arteriography was undertaken in one case (No. 22), because clinically it was considered that the lesion had been lateralized. The findings, merely demonstrated a hydrocephalus, as evidenced by the wide sweep of the pericallosal artery. This was seen to be mid-line in antero-posterior view. A consideration of the pathology makes it clear that no further information could be obtainable by this method. This case again illustrates the difficulty of accurate clinical diagnosis, and the misleading manner in which paraphysial cysts may present themselves.

Case Reports

Case 1.—1934: A. H., male, aged 31. He was admitted to the National Hospital under the care of Sir Charles Symonds with a four months' history of severe headaches. These had become worse and more frequent recently, and were relieved by lying down.

O.E.—There was bilateral papillœdema, but otherwise no significant neurological findings. Lumbar puncture—cerebrospinal fluid pressure 300 mm.; composition normal. Twenty-four hours later the patient became unconscious. Ventricular taps revealed distended lateral ventricles, and were followed by a subtentorial decompression for a supposed posterior fossa lesion. Nil abnormal was found, and the patient died soon after.

Autopsy.—A paraphysial cyst was found. Massive acute infarction of both posterior cerebral arteries was also present.

Radiology.—Plain X-rays which are no longer available for examination were reported as showing no abnormality. No ventriculography was performed.

Case 2.—1936 : M. R., female, aged 45. This case has already been reported by Jefferson (1937). There was a seven years' history of symptoms suggesting intermittent hydrocephalus associated with psychotic symptoms which were probably non-related. Ventriculography established the diagnosis.

Operation—recovery.

Radiology.—(*a*) Plain X-ray showed thinning of the dorsum sellæ consistent with raised intracranial pressure—no localizing signs. (*b*) Ventriculography clearly demonstrated the tumour, and was diagnostic of paraphysial cyst (fig. 8).

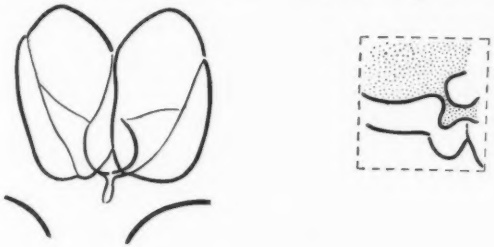

FIG. 8 (*Case* 2)—Ventriculogram tracing.

This case is of historical interest, being the first to be cured at the National Hospital.

Case 3.—1936 : G. H., female, aged 52. This case has already been reported by Jefferson and Jackson (1939). There was a seven months' history of tingling of the scalp, mental dulling, and drowsiness, and a five months' history of headache, sudden falls, and visual deterioration.

O.E.—Low-grade bilateral papillœdema was present. Extrapyramidal rigidity of both arms and the right leg was noted.

Straight X-ray was reported as showing left fronto-parietal bone thickening, and a diagnosis of meningioma was made. A bone flap was turned and no lesion found.

Ventriculography was performed a week later and reported as showing symmetrical dilated lateral ventricles with non-filling of the 3rd ventricle.

The patient became drowsy and, after improving, died suddenly seven days later.

Autopsy.—A typical paraphysial cyst was found (fig. 1).

Radiology.—The films have unfortunately been lost, and cannot therefore be reviewed.

Case 4.—1939 : A. G., male, aged 36. Admitted to the National Hospital under the care of Dr. J. St. C. Elkington and transferred to the care of Mr. Harvey Jackson. The patient had a four months' history of headache with occasional vomiting.

O.E.—The only positive findings were bilateral papillœdema, and a large right pupil which reacted poorly to light.

A 3rd ventricle cyst was diagnosed on ventriculography and removed. Recovery.

Radiology.—(*a*) Plain X-ray showed thinning of the dorsum sellæ indicating raised intracranial pressure. (*b*) Ventriculography was diagnostic (fig. 9).

Case 5.—1939 : W. H., male, aged 42. Admitted to Hurstwood Park Emergency Hospital under the care of Mr. Julian Taylor. Three months previously he began to have occasional attacks of dizziness and frontal headaches. These became more severe and frequent, and were often accompanied by vomiting.

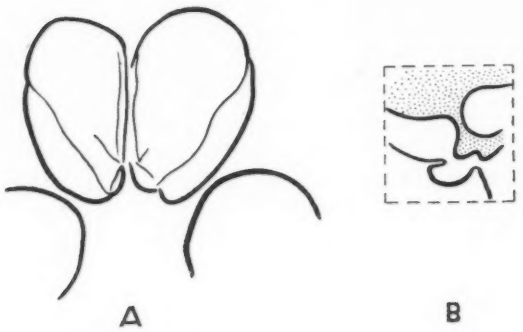

FIG. 9 (*Case* 4).—Ventriculogram tracing.

O.E.—Slight bilateral papillœdema was present. The only other signs found were a doubtful right facial weakness and an indefinite left plantar response. The C.S.F. was at a pressure of 210 mm. of water but its composition was normal. Ventriculography indicated a tumour "in the neighbourhood of the foramina of Monro."

Operation.—A typical paraphysial cyst was removed. The patient made an excellent recovery.

Radiology.—The films are no longer available and cannot be reviewed. The reports stated that: (*a*) Plain X-ray showed "slight flattening of the sella turcica." (*b*) Ventriculography showed symmetrical hydrocephalus with non-filling of the 3rd ventricle. In the "hanging head" lateral view "a well-defined rounded shadow can be seen protruding into the right ventricle from its floor just behind the region of the foramen of Monro."

Case 6.—1939: H. W., male, aged 50. Admitted to the Maida Vale Hospital for Nervous Diseases under the care of Mr. Wylie McKissock, referred by Professor F. Golla. For six months he had complained of a pain in the right side of the head, face and body, and for one month of diplopia and visual deterioration.

O.E.—Bilateral papillœdema was present. Ventriculography showed a gross symmetrical hydrocephalus which was thought to be due to a posterior fossa lesion.

Operation.—A posterior fossa decompression was performed, and the patient died shortly after.

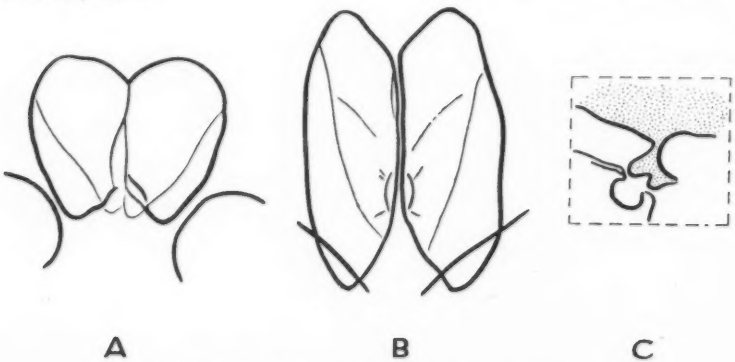

FIG. 10 (*Case* 6).—Ventriculogram tracing.

Autopsy.—A paraphysial cyst was found.

Radiology.—(*a*) Plain X-ray revealed no abnormality. (*b*) Ventriculography: The films which were misinterpreted at the time are diagnostic (fig. 10).

Case 7.—1942: E. R., male, aged 48. Admitted to the Maida Vale Hospital for Nervous Diseases under the care of Mr. Wylie McKissock, referred by Dr. Wilfred Harris. There was one year's history of fits and headaches.

O.E.—Slight bilateral papillœdema was present, but no other positive neurological signs. Lumbar puncture showed the C.S.F. pressure to be 220 mm. of water. Ventriculography revealed the cyst.

Operation—recovery.

Radiology.—(*a*) Plain X-ray was normal. (*b*) Ventriculography was diagnostic (fig. 11).

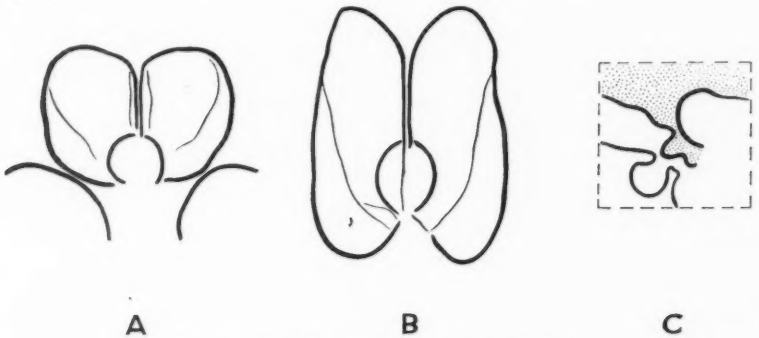

FIG. 11 (*Case* 7).—Ventriculogram tracing.

Case 8.—1944: L. M., female, aged 26. Admitted to the Atkinson Morley Hospital under the care of Mr. Wylie McKissock, referred by Dr. J. St. C. Elkington. She had a history of intermittent headache for four and a half years, and of weakness and paræsthesiæ of the right arm and leg for one year. Unsteadiness on walking had been present for six months with recent giddy attacks. Mistiness of vision had been noted for one month.

O.E.—Bilateral papillœdema, and a slight right facial weakness were found, and her gait was slow and unsteady. No Rombergism. Lumbar puncture—normal fluid and pressure. Ventriculography revealed the cyst.

Operation—recovery.

Radiology.—(*a*) Plain X-ray: Thinning of the dorsum sellæ suggesting generally raised intracranial pressure. (*b*) Ventriculography was diagnostic (fig. 12.)

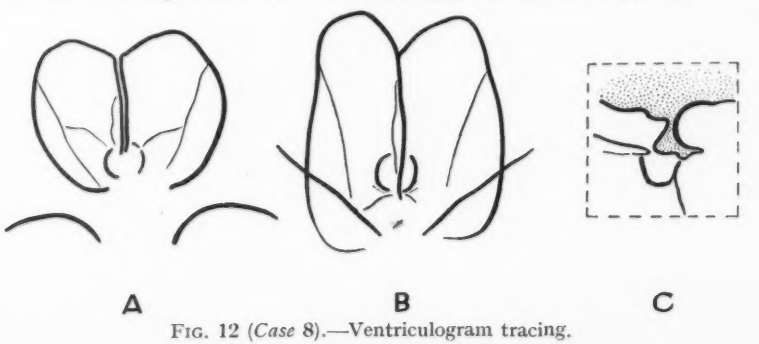

FIG. 12 (*Case* 8).—Ventriculogram tracing.

Case 9.— 1945 : L. C., male, aged 29. Admitted to the Atkinson Morley Hospital under the care of Mr. Wylie McKissock, referred by Dr. J. St. C. Elkington. The patient had a nine months' history of headaches and of transient weakness of the legs. Vomiting had been present in the past two months.

O.E.—No positive neurological findings. *C.S.F.* pressure 280 mm. of water, falling to 140 on removing 5 c.c.—normal composition. Plain X-rays were negative. Discharged for out-patient observation. Two months later he was readmitted after recurrence of the attacks in a more severe form. Papillœdema was now present. Ventriculography showed the cyst.

Operation—recovery after a stormy convalescence.

Radiology.—(*a*) Plain X-ray was normal. (*b*) Ventriculography was diagnostic (fig. 13).

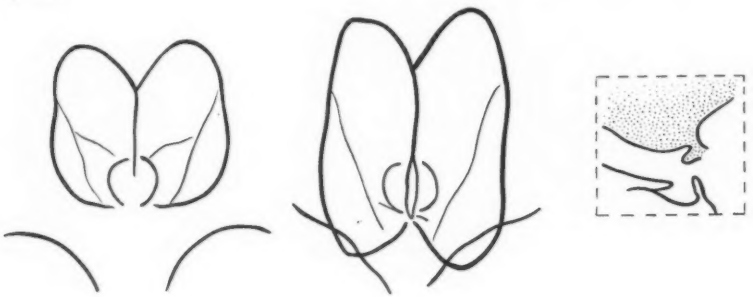

FIG. 13 (*Case* 9).—Ventriculogram tracing.

Case 10.—1945 : M. C., female, aged 25. Admitted to the Atkinson Morley Hospital under the care of Mr. Wylie McKissock, referred by Dr. F. M. R. Walshe. Two years' history of occipital headaches. Occasional diplopia and blurring of vision. Memory impaired.

O.E.—Moderate papillœdema was noted. Otherwise no neurological signs. Diagnosed on ventriculography. Cyst removed at operation, but the patient died three days later.

Autopsy.—Post-operative hæmorrhages throughout the ventricular system.

Radiology.—(*a*) Plain X-ray showed thinning of the dorsum sellæ consistent with raised intracranial pressure. (*b*) Ventriculography was diagnostic (fig. 14).

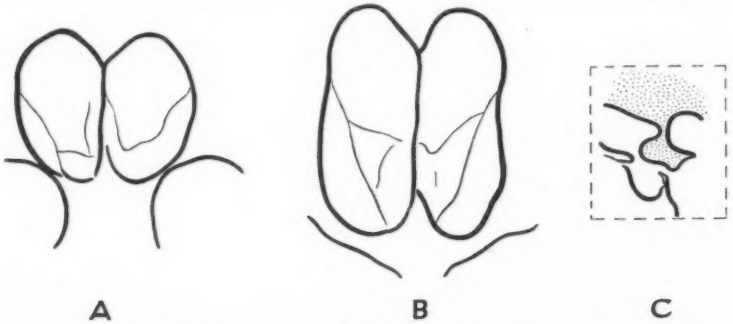

FIG. 14 (*Case* 10).—Ventriculogram tracing.

Case 11.—1946 : B. C., male, aged 35. Admitted to the Atkinson Morley Hospital under the care of Mr. Wylie McKissock, referred by Dr. Anthony Feiling. There was one year's history of headache associated with weakness of the legs.

O.E.—Bilateral papillœdema. Otherwise no abnormal signs. Diagnosed on ventriculography. An attempt at operative removal was complicated by hæmorrhage and failure of the suction apparatus which led to excessive operative trauma. The patient died seven days after operation.

Histology at the time was reported as showing a "squamous epitheliomatous cyst." Review now conclusively proves the cyst to be paraphysial.

Radiology.—(*a*) Plain X-ray showed sellar enlargement consistent with generally raised intracranial pressure. (*b*) Ventriculography was diagnostic (fig. 15).

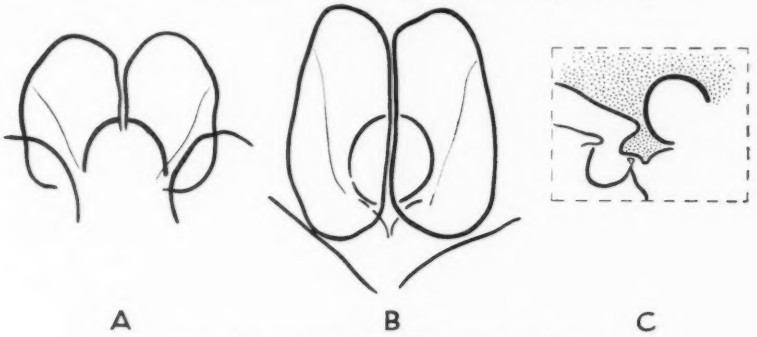

FIG. 15 (*Case* 11).—Ventriculogram tracing.

Case 12.—1946 : E. W., female, aged 38. The patient was admitted to the National Hospital under the care of Mr. Harvey Jackson. There was an eight years' history of headaches, becoming worse in the past two years, with occasional vomiting. Attacks of left-sided facial numbness and loss of consciousness. Eighteen months' defective vision. In 1945 she was investigated as an in-patient with no diagnosis being arrived at. Encephalography failed to fill the ventricular system. She was readmitted in 1946.

O.E.—Bilateral papillœdema. Absent left corneal reflex. Diagnosis was made by ventriculography.

Operation—the cyst was removed, but the patient died four days later.

Autopsy.—Hæmorrhage into lateral and 3rd ventricles.

Radiology.—(*a*) Plain X-ray showed sellar enlargement and the dorsum sellæ thinned. (*b*) Ventriculography was diagnostic (fig. 16).

Case 13.—1947 : N. H., male, aged 31. He was admitted to the National Hospital under the care of Dr. J. Purdon Martin and transferred to the care of Mr. Wylie McKissock. He complained of failing vision, his only symptom, for the previous nine months. Clinically he was regarded as a possible suprasellar tumour.

O.E.—Bilateral papillœdema, and a left nasal field defect were noted. Otherwise there were no abnormal findings. Lumbar puncture showed cerebrospinal fluid normal in composition but under a pressure of 300 mm. of water. Ventriculography gave the diagnosis.

Operation—the cyst was removed and the patient recovered.

Radiology.—(*a*) Plain X-ray was normal. (*b*) Ventriculography was diagnostic (fig. 17).

Case 14.—1947 : F. C., male, aged 40. He was admitted to the National Hospital under the care of Dr. F. M. R. Walshe and transferred to the care of Mr. Wylie McKissock. For two years he had suffered from bifrontal headaches, becoming

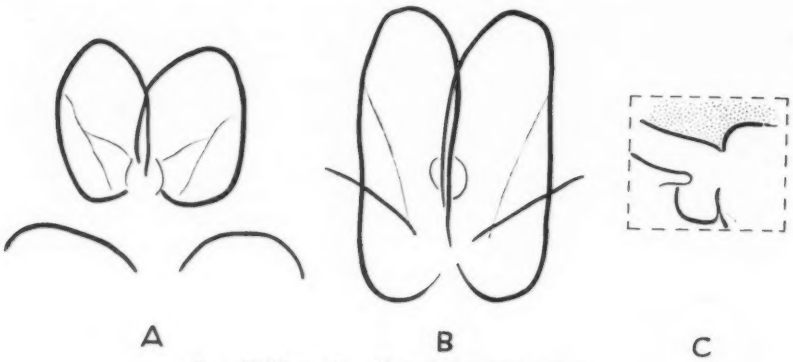

FIG. 16 (*Case* 12).—Ventriculogram tracing.

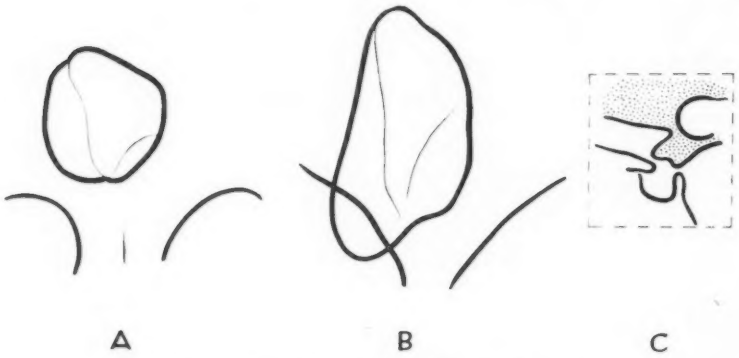

FIG. 17 (*Case* 13).—Ventriculogram tracing.

worse and more frequent recently. He had been incontinent of fæces on two occasions in the past few months. Tiredness and inability to concentrate had been present for some weeks.

O.E.—Slight blurring of the right optic disc ; plantar reflexes indefinite ; otherwise no abnormal findings. Cerebrospinal fluid pressure 250 mm., but normal composition. E.E.G. was normal. Diagnosis made by ventriculography.

Operation—followed by recovery.

Radiology.—(*a*) Plain X-ray showed thinning of the dorsum sellæ consistent with raised intracranial pressure, but no localizing signs. (*b*) Ventriculography was diagnostic (fig. 18).

Case 15.—1948 : J. H., male, aged 41. Admitted to the National Hospital under the care of Dr. Denis Brinton and transferred to the care of Mr. Wylie McKissock. Seven years ago he had had attacks of numbness and pins and needles in the left arm, and in the next four years occasional severe headaches, and several attacks of loss of consciousness. His symptoms ceased three years ago, and he was well until the onset of the present illness. For the past twelve months he had complained of (1) weakness of the left arm, (2) frequency of micturition, (3) apathy, lethargy, and somnolence, which led to his losing his job.

O.E.—Slight papilloedema, and a slight left facial weakness were found. Reflexes brisk on the left side. Doubtful left extensor plantar response. Cerebrospinal

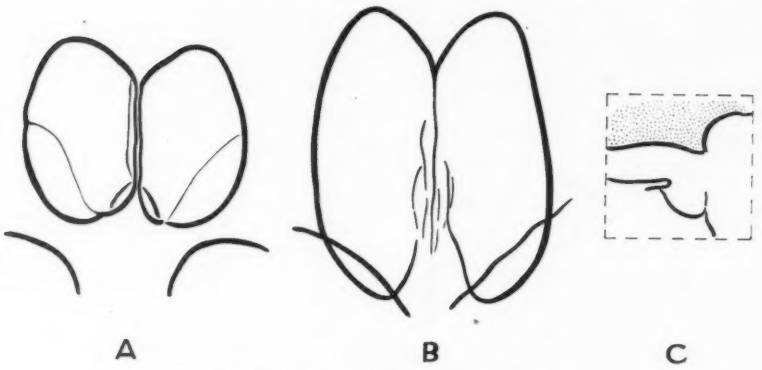

FIG. 18 (*Case* 14).—Ventriculogram tracing.

fluid normal in composition but pressure 250 mm. of water. Clinically he was regarded as a possible right frontal neoplasm. Ventriculography gave the diagnosis.

Operative removal of the cyst was followed by recovery.

Radiology.—(*a*) Plain X-ray was normal. (*b*) Ventriculography was diagnostic (fig. 19).

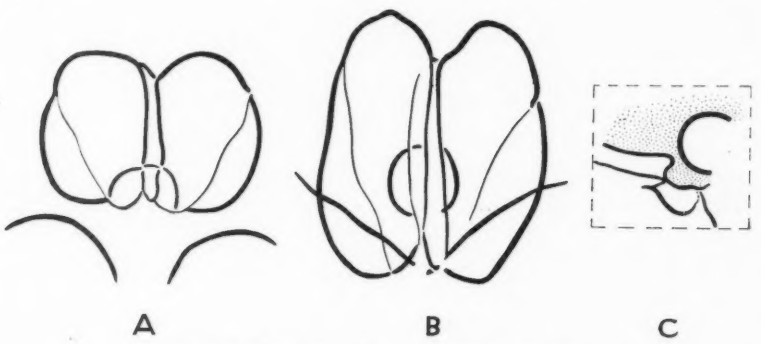

FIG. 19 (*Case* 15).—Ventriculogram tracing.

Case 16.—1948: A. E., male, aged 42. He was admitted to the National Hospital under the care of Mr. Wylie McKissock. There was one and a half years' history of intermittent attacks of occipital headache, relieved by lying down. Weakness and pain in the right arm were also present. The attacks had been associated with giddiness and blurring of vision in the past few months.

O.E.—Bilateral papillœdema with hæmorrhages and early optic atrophy. Ventriculography showed symmetrical hydrocephalus with non-filling of the 3rd ventricle. A bilateral Torkildsen operation was performed soon after. Myodil ventriculography was performed and showed complete blockage of the foramina of Monro, and the diagnosis remained doubtful.

Operation.—A paraphysial cyst was exposed and removed. He died a week later after a stormy post-operative course.

Autopsy showed blood clot in the lateral ventricles and in the aqueduct, apparently causing blockage of the latter.

Radiology.—(*a*) Plain X-ray showed no abnormal findings. (*b*) Ventriculography : Careful examination including myodil ventriculography failed to outline the tumour. However the radiological diagnosis of " obstructive lesion at the foramen of Monro " in association with an unusually typical history were strongly suggestive of a paraphysial cyst (fig. 20).

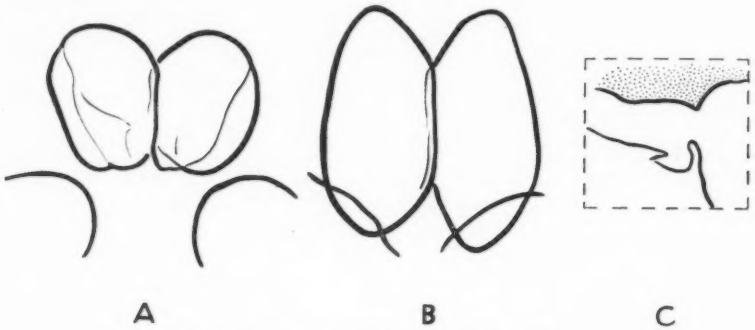

FIG. 20 (*Case* 16).—Ventriculogram tracing.

Case 17.—1948 : K. L., male, aged 35. He was admitted to the National Hospital under the care of Dr. Michael Kremer with a seven days' history of severe frontal headache with vomiting. He was drowsy and disoriented on admission and soon became comatose. An emergency right ventricular tap revealed a dilated ventricle, but the patient died soon after.

Autopsy.—A paraphysial cyst was found blocking the foramina of Monro. There was hydrocephalus of the lateral ventricles, and there were petechial hæmorrhages in the pons.

Radiology.—No X-rays were taken owing to the patient's grave condition.

Case 18.—1948 : I. H., female, aged 45. Admitted to the National Hospital under the care of Sir Charles Symonds, and transferred to the care of Mr. Wylie McKissock. There was a five years' history of " attacks," in which she fell over backwards but was not unconscious. She also complained of occipital headaches with vomiting, and of generalized pains in the joints. There was paresis of the lower limbs, with difficulty in walking, severe eighteen months ago, but improving later. Mental dulling was noted and she had been incontinent of urine for the past year. Her weight was increasing.

O.E.—Seven months ago she was noted to have extensor plantar responses and spastic lower limbs. No papillœdema. C.S.F.—normal pressure and composition. Ventriculography showed symmetrical hydrocephalus with non-filling of the 3rd ventricle. A diagnosis of 3rd ventricle tumour was made. Surgical intervention was not considered advisable, and X-ray therapy was advised. On leaving hospital the patient improved temporarily, but relapsed. Fortunately she did not undergo therapy.

At second admission—no fresh findings. Ventriculography on this occasion resulted in a definite diagnosis of paraphysial cyst.

Operation—recovery.

Radiology.—(*a*) Plain X-ray considered normal. (*b*) Ventriculography : The first series had been interpreted as above, but review shows that the cyst is visualized in antero-posterior view. The second series were also diagnostic of a paraphysial cyst (fig. 21, A, B, and C). Post-operative ventriculogram showed a normal 3rd ventricle (fig. 21D).

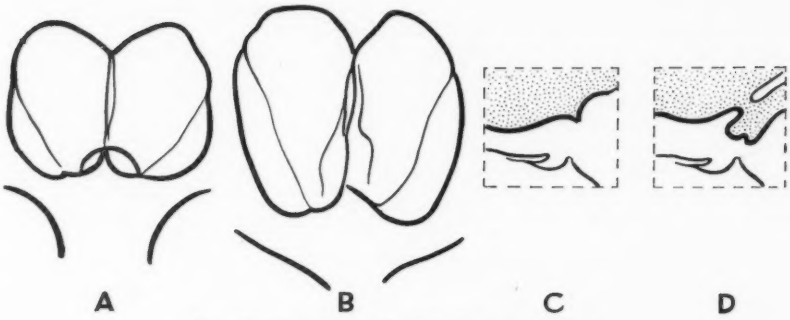

FIG. 21 (*Case* 18).—Ventriculogram tracing.

Case 19.—1948: E. H., male, aged 38. Admitted to the National Hospital under the care of Sir Charles Symonds and transferred to the care of Mr. Wylie McKissock. He was perfectly well till five months ago when he began to have attacks of giddiness with blurring of vision in the left eye several times a day. Soon after he had early morning frontal headaches lasting a few hours. He was symptom free for five weeks. Then there was a recurrence with more severe headaches and blurring of vision. Finally weakness of both legs came on and he had continuous headaches for four weeks.

O.E.—Definite papillœdema of left disc. Right disc indefinite. Otherwise no positive neurological findings. Clinically considered as a possible left frontal neoplasm. C.S.F. was normal. Ventriculography gave the diagnosis.

Operation.—The cyst was difficult to remove, but it was punctured and the contents squeezed out and sucked away. Recovery.

Radiology.—(*a*) Plain X-ray: No abnormal findings. (*b*) Ventriculography: Only the left lateral ventricle was filled. Manipulation failed to fill the right lateral ventricle, but the anterior end of the 3rd ventricle was filled. It was not dilated, and a semilunar defect was visible. Myodil was used to confirm this, but it failed to enter the 3rd ventricle.

Conclusion.—Paraphysial cyst (fig. 22).

Case 20.—1948: J. A. L. C., male, aged 34. Admitted to the National Hospital under the care of Dr. Denis Williams and transferred to the care of Mr. Harvey Jackson. Nine years ago he had a sudden attack of loss of consciousness followed

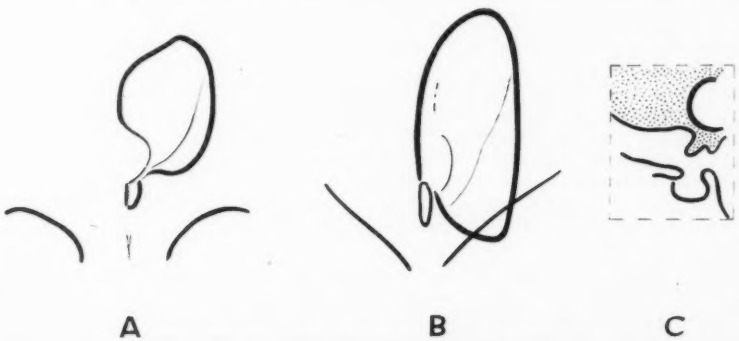

FIG. 22 (*Case* 19).—Ventriculogram tracing.

by headache and vomiting, and was off work for a week. He was then quite well till five years ago when he began to have attacks of headache and vomiting about once a month. These went on for seven or eight months, when they ceased for about six months. Four years ago they recurred in a more severe and frequent form, now accompanied by attacks of loss of consciousness. The symptoms lasted about six months, and were again followed by six months' freedom. During the last three years several similar periods of " attacks " followed by remissions occurred.

For the previous six months he had noticed deterioration of vision, particularly in the right eye. Memory and powers of concentration had been impaired for the previous three or four years, and libido had been diminished for the last eighteen months.

O.E.—Bilateral papillœdema was present, more marked on the right. There was some weakness of the left arm and leg, and a doubtful extensor plantar on the left side. No other positive findings.

A Torkildsen operation was first performed, as the surgeon was not convinced of the diagnosis. Later, however, operation was undertaken, and a paraphysial cyst successfully removed.

Radiology.—(*a*) Plain X-ray showed nil abnormal. (*b*) Ventriculography was in our opinion diagnostic of paraphysial cyst (fig. 23).

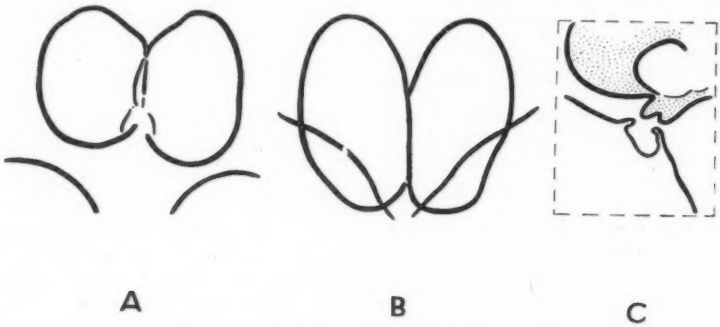

FIG. 23 (*Case* 20).—Ventriculogram tracing.

Case 21.—1947: M. P., female, aged 34. (Case of Mr. J. E. A. O'Connell.) Twelve months' history of attacks of headache, becoming increasingly severe. At first frontal, but later generalized. Six months' history of associated vomiting, and for past few months of " silver specks floating before the eyes." Had recently become apathetic and slovenly. An attack of unconsciousness lasting one hour occurred in hospital.

O.E.—Marked bilateral papillœdema. Pupillary reflex sluggish. Paralysis of upward gaze. Head held flexed to the right and with occiput to the right, but this neck rigidity was not persistent. No other abnormal signs.

A provisional diagnosis of a posteriorly placed 3rd ventricle tumour was made.

Ventriculography showed obstruction at the foramina of Monro.

At operation a cyst was removed from the right foramen of Monro. Despite its situation its yellowish appearance suggested to the surgeon a dermoid rather than a colloid cyst.

Histologically, however, the tumour proved to be a definite paraphysial cyst, and not a dermoid.

Radiology.—(*a*) Plain X-ray showed nil abnormal. (*b*) Ventriculography : No air has entered the 3rd ventricle, but we consider the A.P. brow-up film to be diagnostic of paraphysial cyst (fig. 24).

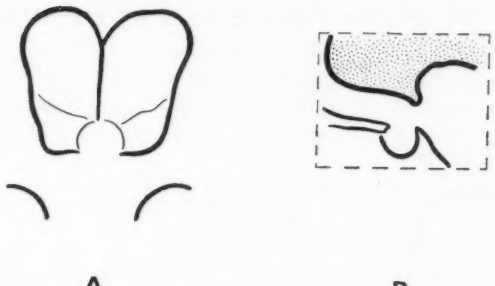

FIG. 24 (*Case* 21).—Ventriculogram tracing.

Case 22.—1948: M. F., female, aged 43. Admitted to the Atkinson Morley Hospital under the care of Mr. Wylie McKissock. Severe bifrontal headaches commenced six years ago. Visual acuity had deteriorated over the past four years. In the previous year she had had frequent "blackouts," sometimes with incontinence. In the previous five weeks there had been two periods of unconsciousness lasting several hours, and difficulty in standing or walking had been noted recently.

O.E.—Appeared mentally dull and slightly drowsy. Moderate bilateral papilloedema. Slight left lower facial weakness. Doubtful left pyramidal signs. Gait unsteady. Hypertension without cardiac involvement. C.S.F. was normal in pressure and content.

The case was at first regarded as a left hemisphere lesion, and arteriography was undertaken.

Ventriculography was diagnostic, but the films were seen by a colleague who proceeded with myodil ventriculography hoping to clinch it. Successful operative removal.

Radiology.—(*a*) Plain X-ray—evidence of raised intracranial pressure without localizing signs. (*b*) Arteriography showed a hydrocephalus. (*c*) Ventriculography was diagnostic. Myodil gave no further information (fig. 25).

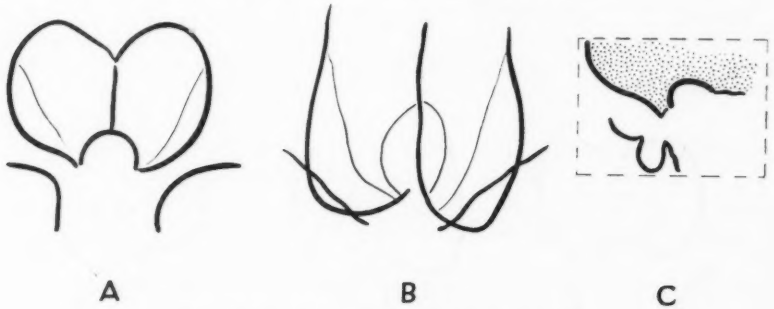

FIG. 25 (*Case* 22).—Ventriculogram tracing.

Case 23.—1949: M. D. C.-B., male, aged 40. Admitted to the Atkinson Morley Hospital under the care of Mr. Wylie McKissock, and referred by Dr. P. H. Sandifer. The patient had a three-weeks history of occipital headache associated with nausea.

O.E.—The left pupil was slightly irregular, but there were no other abnormal clinical findings and the fundi were considered normal. Lumbar puncture performed

at another hospital showed a cerebrospinal fluid pressure of 300 mm. Ventriculography gave the diagnosis.

Operation.—followed by recovery.

Radiology.—(*a*) Plain X-rays suggested early pressure changes in the posterior clinoids and dorsum sellæ. (*b*) Ventriculography was diagnostic of a paraphysial cyst (fig. 26).

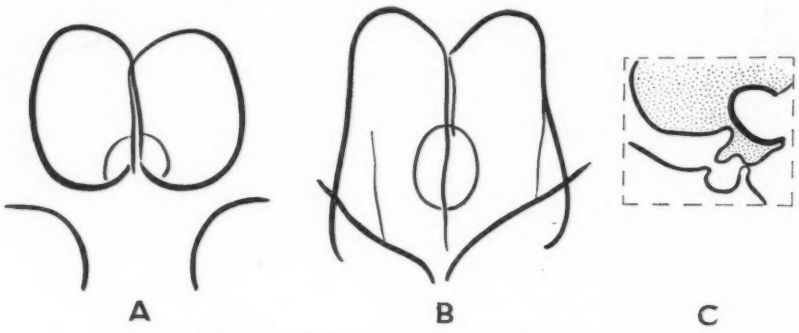

FIG. 26 (*Case* 23).—Ventriculogram tracing.

Case 24.—1949 : F. K., male, aged 26. Admitted to the National Hospital under the care of Dr. Swithin Meadows and transferred to the care of Mr. Wylie McKissock. He had suffered from headaches for the previous three months, and these had been associated with vomiting in the last two months.

O.E.—Bilateral chronic papillœdema with hæmorrhages and a very little exudate. The left pupil was slightly larger than the right and both pupils reacted sluggishly to light and convergence. Clinically he was regarded as a possible cerebellar tumour. There were no other positive clinical findings. Ventriculography gave the diagnosis.

Operation.—Recovery. In addition to the paraphysial cyst a small unsuspected right subdural hæmatoma was encountered and evacuated.

Radiology.—(*a*) Plain X-rays were considered to be normal. (*b*) Ventriculography was diagnostic with " hanging head " lateral and antero-posterior films, although air filling did not reach the foramina of Monro in the brow-up position (figs. 6 and 27).

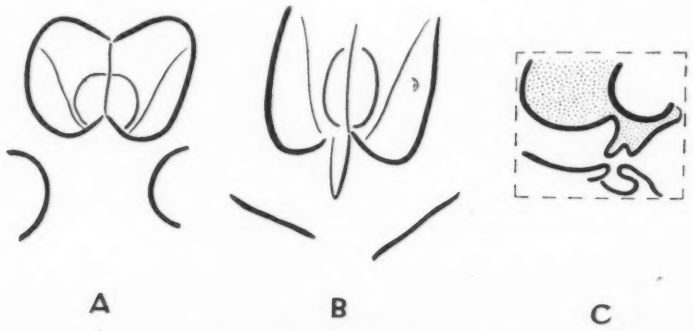

FIG. 27 (*Case* 24).—Ventriculogram tracing.

Differential Diagnosis

The above case-records make it clear that the positive diagnosis of paraphysial cyst can be made by ventriculography in all but exceptional cases.

In the differential diagnosis two groups of lesions must be considered, viz.

(1) Tumours lying in the 3rd ventricle.

(2) Tumours adjacent to the 3rd ventricle and encroaching on it.

Both these groups may give rise to a ventriculographic picture of symmetrical hydrocephalus with or without some air in the 3rd ventricle which may superficially resemble the pathognomonic picture we have described. We believe that difficulty in coming to a definite diagnosis should rarely be encountered except in the cases where there is a complete failure to introduce any air into the 3rd ventricle.

(1) *Tumours lying in the 3rd ventricle.*—Though tumours lying in the 3rd ventricle have been described by Dandy (1933) by Jefferson and Jackson (1939) and by others, true intraventricular tumours must be considered rare entities.

The question of so-called *3rd Ventricle Dermoids* has already been discussed. Though accepting the theoretical possibility that a dermoid cyst might originate in exactly the same position as the paraphysial cysts, we agree with Grossiord that the few cases published as such cannot be accepted as true dermoids and must be regarded as paraphysial cysts on histo-pathological grounds.

This view is given strong support by the review of Cases 11 and 21 reported above.

Meningioma has been described as occurring in the 3rd ventricle (Cushing and Eisenhardt, 1938 ; Jefferson and Jackson, 1939 ; Lysholm, 1948). The tumour is usually large and occupies the whole lumen of the ventricle. In none of the above cases could the tumour have reasonably been mistaken for a paraphysial cyst, although Lysholm (1948) suggested that differential diagnosis was not possible. The occurrence of calcification in Cushing and Eisenhardt's cases is another distinguishing feature. We think, however, that theoretically a 3rd ventricle meningioma of the right size, shape and position could simulate a paraphysial cyst, and of course the diagnosis would remain in doubt if the 3rd ventricle failed to fill, and ventriculography merely revealed a symmetrical hydrocephalus of the lateral ventricles.

Choroid cysts in the 3rd ventricle have not been encountered by us, but again theoretically could simulate a paraphysial cyst.

Parasitic cysts must also be considered in the diagnosis. Ectors (1941) has published an interesting example of a Cysticercus cyst in the 3rd ventricle which closely resembles a paraphysial cyst ventriculographically. Two other cases are described by Allen and Lovell (1932).

The possibility of a *Pituitary Anlage cyst* (Syn. Adamantinoma, Craniopharyngioma) lying entirely in the 3rd ventricle was raised by Jefferson

and Jackson (1939). Calcification if present would help in the differential diagnosis which would otherwise prove difficult. Such a case is reported by Zeitlin and Oldberg (1940).

Papillomas may arise from the roof of the 3rd ventricle, as well as in the 4th ventricle and lateral ventricles (Van Wagenen, 1930; Posey, 1942). We have not encountered a 3rd ventricle papilloma, but we doubt if accurate preoperative diagnosis in such a case would be possible.

Ependymoma has also been described as occurring in the 3rd ventricle (Allen and Lovell, 1932; Twining, 1939; Jefferson and Jackson, 1939; Chusid, 1948; Lysholm, 1948).

Most cases described have shown a localization at the back of the ventricle, with blockage of the mouth of the iter. The resultant 3rd ventricle dilatation should be readily distinguishable from the paraphysial cyst picture. In one case seen by us the 3rd ventricle was completely filled and blocked by an ependymoma.

(2) *Tumours adjacent to the 3rd ventricle.*—The other group of tumours mentioned, those arising near the 3rd ventricle and encroaching on it, must now be considered. The differential diagnosis in these cases should not be difficult, *provided the 3rd ventricle contains air*, on account of the very different ventricular deformities produced. We would emphasize again therefore the necessity for an adequate technique in which every attempt is made to obtain filling of the 3rd ventricle.

Tumours lying in front of the 3rd ventricle will indent the optic and infundibular recesses and press upon the lamina terminalis. Thus *suprasellar meningiomas* and *aneurysms* cannot possibly be confused with paraphysial cysts. Sellar and suprasellar tumours (except the rare type already discussed) again give quite a different picture. They press up the floor of the 3rd ventricle and fail to show forward displacement of the foramina of Monro. Glioma of the caudate nucleus may give a fairly similar picture.

A remarkable case of Tuberous Sclerosis in which the ventriculographic picture was similar to that of a case of paraphysial cyst was published by Twining (1939*b*) and is also reported by Jefferson and Jackson (1939). The tumour shown was definitely anterior to the foramina of Monro. Diagnosis was possible on clinical grounds, and because of a characteristic intracranial calcification.

We have recently seen an almost identical case. The ventriculographic appearances strongly resembled those of Twining's case, and suggested the possibility of a paraphysial cyst. Careful examination, however, showed that the foramina of Monro were posterior and not anterior to the tumour. The 3rd ventricle could not be filled with air. The lesion also projected rather more to one side of the mid-line than is the case with paraphysial cysts. Plain X-ray showed several small discrete areas of calcification and was diagnostic of tuberous sclerosis. The patient also had characteristic skin lesions, and the diagnosis was confirmed at autopsy.

Lesions pressing on the 3rd ventricle behind the foramina of Monro should not be confused with paraphysial cysts. The features of the various types are briefly described as follows :

(*a*) *Glioma of the optic thalamus* produces a filling defect in the body or posterior part of the ventricle or may even obstruct the foramina (considered below). Sometimes it causes the 3rd ventricle to become crescent shaped in antero-posterior view. The convexity of the crescent bends to the opposite side. In lateral view the shadow of the air-fluid junction against the tumour may be irregular in shape, an appearance never seen in paraphysial cyst.

(*b*) *Pineal tumours* have also been considered in the differential diagnosis, probably on account of the sharp crescentic filling defect they cause in the 3rd ventricle seen in lateral view. This defect can only be confused with that caused by a paraphysial cyst if it lies very far forward. Even then it should not be confused because the foramina are not displaced forwards, and because hydrocephalus of the 3rd ventricle is present, with dilation, and not narrowing of the foramina of Monro.

(*c*) *Tumours of the corpora quadrigemina* may produce a filling defect on the posterior part of the 3rd ventricle very similar to that produced by a pineal tumour, but 3rd ventricle hydrocephalus is always present.

Lesions farther back still, such as aqueduct stenosis or pontine tumours are so unlike paraphysial cysts radiologically that discussion need not be further pursued.

Non-filling of the 3rd ventricle.—Turning now to tumours obliterating the 3rd ventricle and causing complete obstruction of the foramina of Monro we cannot be so precise.

Theoretically any lesion growing from the sellar neighbourhood can produce such a picture, and only judgment, experience and general assessment of the case can get one nearer the diagnosis.

Pituitary anlage cysts and other pituitary tumours may give such an appearance (*v.* Cases A and B). A large *suprasellar meningioma* may cause complete obliteration of the 3rd ventricle, as in a case recently seen by one of us.

Of the other causes gliomata of the caudate nucleus and thalamus are the most likely.

The intraventricular tumours discussed above might also obliterate the 3rd ventricle, and in such cases ventriculography could not provide a definite diagnosis.

The following 2 cases are reported as examples illustrating complete obstruction of the foramina of Monro by tumour pressing up from below.

Although, as we have shown, a careful ventriculographic technique should rarely fail to demonstrate a paraphysial cyst, cases will occur (as No. 16) where the diagnosis remained in doubt. Radiologically such cases cannot be differentiated from other obstructive lesions at the foramina of Monro such as the following, but the possibility of a benign lesion to our mind justifies exploration of these cases.

Case Reports

Case A.—1948 : W. A. O., male, aged 31. Admitted to the National Hospital under the care of Mr. Harvey Jackson. The patient had a four years' history of failing vision. Severe headaches had been present for five weeks.

O.E.—Bilateral papillœdema, and a slight right lower facial weakness were noted. Otherwise there were no abnormal clinical findings. Ventriculography demonstrated an obstruction at the foramina of Monro. After ventriculography the patient's condition gradually deteriorated, and he died twenty-four hours later.

Autopsy.—A large bilocular suprasellar cyst was found occluding the 3rd ventricle from below.

Histology—Pituitary anlage cyst (fig. 28).

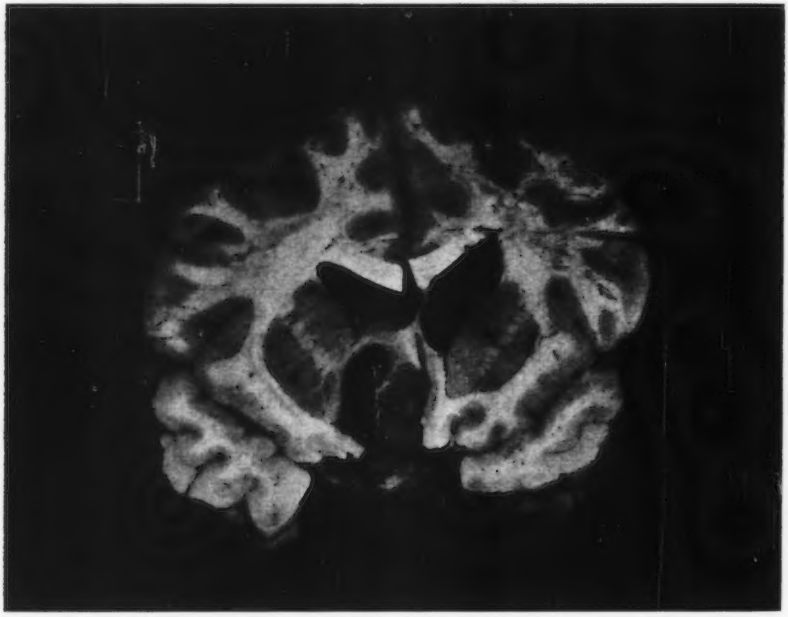

Fig. 28 (*Case A*).—Loculated suprasellar cyst occluding the 3rd ventricle. The pushing up of the floor of the right lateral ventricle was not apparent in the air studies which merely showed a symmetrical hydrocephalus.

Radiology.—(*a*) Plain X-ray. Evidence of generally raised intracranial pressure—no localizing signs. No calcification was present.

(*b*) Ventriculography—Symmetrical hydrocephalus with non-filling of the 3rd ventricle. Diagnosis of " Obstructive lesion at foramina of Monro " (fig. 29).

Case B.—1948 : H. P., male, aged 42. Admitted to the Atkinson Morley Hospital under the care of Mr. Wylie McKissock. There was a history of increasing weight for the previous fifteen months, and of complete loss of libido for the previous year. Mental dulling had been present for three months, and six weeks ago two brief blackouts occurred. For two weeks severe headache with vomiting had been noted and he eventually became delirious and drowsy.

Examination was difficult but his plantar responses were extensor. No papill-

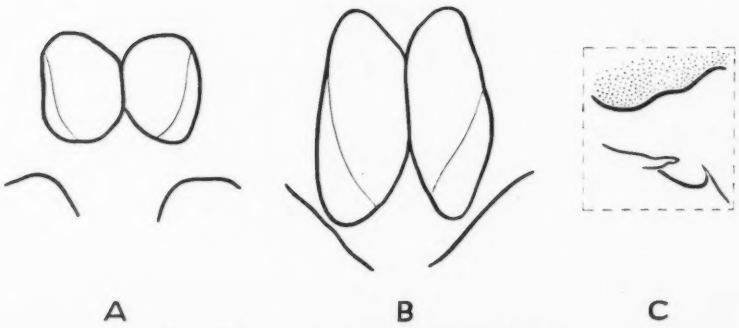

FIG. 29 (*Case A*).—Ventriculogram tracing.

œdema was noted. Ventriculography was inconclusive—" ? colloid cyst. ? expanding lesion below foramen of Monro."

Operation.—No cyst was found and the patient died soon after.

Autopsy.—A growth was found arising from the hypothalamic region and infiltrating the right thalamus, displacing and occluding the anterior part of the 3rd ventricle (fig. 30).

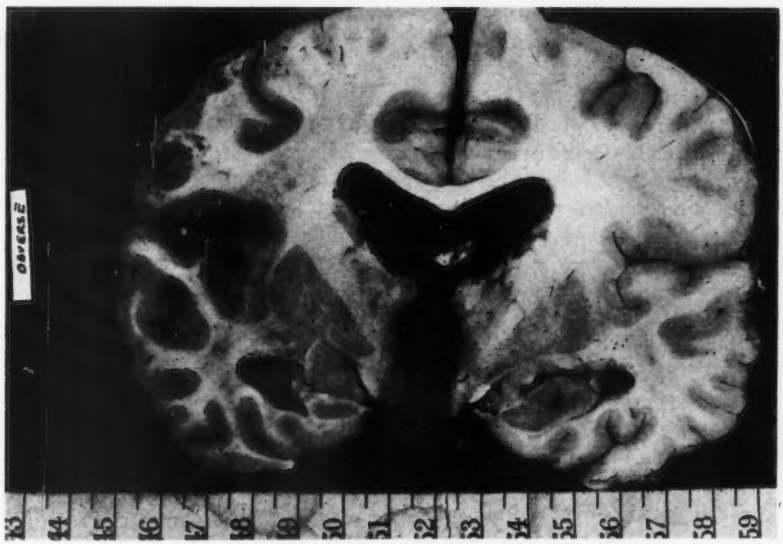

FIG. 30 (*Case B*).—Coronal section through the brain to show symmetrical dilatation of the lateral ventricles, and obliteration of the 3rd ventricle by the tumour.

Histology.—Pituitary adenocarcinoma.

Radiology.—(*a*) Plain X-ray—signs of generally increased intracranial pressure were present.

(*b*) Ventriculography—as below (fig. 31).

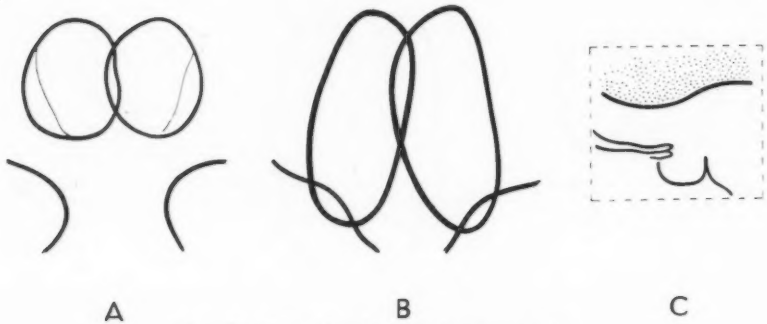

FIG. 31 (*Case B*).—Ventriculogram tracing.

SUMMARY AND CONCLUSIONS

Paraphysial cysts are uncommon tumours though, in our experience, less rare than a review of the literature suggests. 14 of our 24 cases have been seen in the last three years. Though the lesion is relatively uncommon it is completely benign histologically and is surgically accessible. The great importance of accurate diagnosis is therefore obvious. Clinical methods alone cannot provide an accurate diagnosis, though in some cases the history and signs have been suggestive of the nature of the lesion. In the present state of our knowledge we must therefore rely for diagnosis on ventriculography.

For this reason we have made this investigation the main feature of the paper. Of our 24 recorded cases, 22 have not been reported previously : we believe this is the largest single series yet collected. The difficulties of a confident clinical diagnosis are emphasized. It is demonstrated by an analysis of the ventriculograms of 20 cases that a diagnosis of paraphysial cyst can be made in all but very exceptional cases. In only one case examined by us personally were we unable to make the specific diagnosis.

The technique and the radiological differential diagnosis have been discussed at some length, including both rare intraventricular and paraventricular lesions. Though Dandy wrote a book on tumours of the 3rd ventricle, we feel strongly that paraphysial cyst is *the* tumour of the 3rd ventricle. Other tumours in this ventricle are so rare as to be almost museum pieces and the remainder should, in our view, be classified as para-3rd ventricle tumours.

Finally, we feel that a fuller realization and understanding of the radiological possibilities will lead to a more frequent and confident diagnosis of the lesion, which is much commoner than is generally appreciated.

We wish to express our thanks to the clinicians mentioned in the text for permitting us to make use of their case-records and reports, and in particular to Mr. Wylie McKissock, under whose care the majority of the cases were.

Our thanks are also due to Dr. J. G. Greenfield for kindly permitting us to reproduce several photographs and for some stimulating discussions on the pathology of paraphysial cysts.

Postscript

In the intervening period between the completion of the manuscript and the reading of the proofs (about 9 months) we have personally observed another five cases of paraphysial cyst. Three of these were successfully operated on by Mr. Wylie McKissock and two by Mr. Valentine Logue. In all of these a specific diagnosis was made by ventriculography. The total number of cases seen by us personally over a period of four years is therefore seventeen, of which, all but one showed a pathognomonic ventriculographic picture.

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LEGENDS TO ILLUSTRATIONS

FIG. 1A (*Case* 3).—Sagittal section of the brain showing the cyst in situ.

FIG. 1B.—The same specimen seen from above before complete sectioning (Photographs reproduced by courtesy of Dr. J. G. Greenfield).

FIGS. 2A and 2B.—Showing excised paraphysial cysts from Cases 7 and 10 respectively. (By courtesy of Mr. Wylie McKissock.)

FIGS. 3, 4, and 5.—For explanation *see* text.

PLATE XVII

FIG. 1A

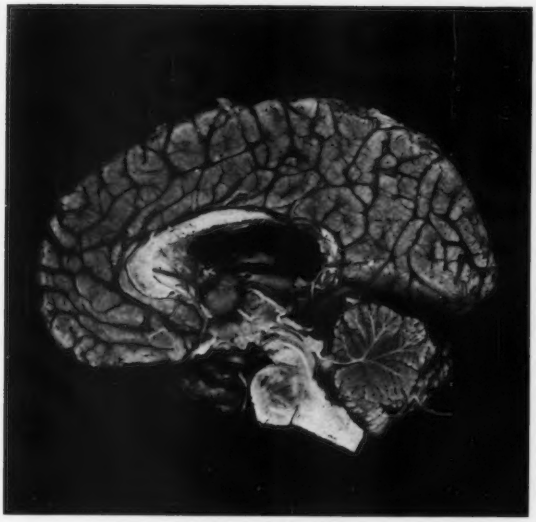

FIG. 2A

FIG. 1B

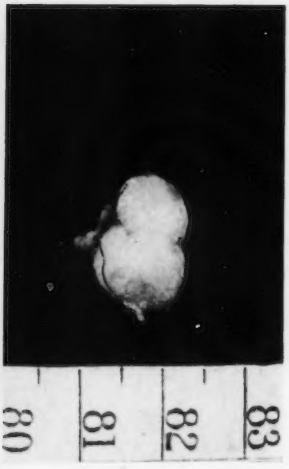

FIG. 2B

To illustrate article by James W. D. Bull and David Sutton.

PLATE XVIII

FIG. 3

FIG. 4

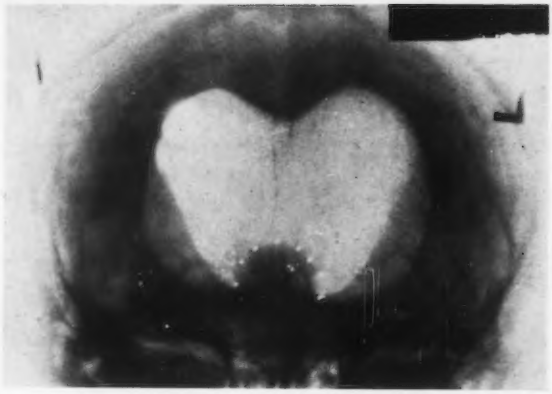

FIG. 5

To illustrate article by James W. D. Bull and David Sutton.

EXPERIMENTAL "ALLERGIC" ENCEPHALOMYELITIS

II.—ON THE NATURE OF THE ENCEPHALITOGENIC AGENT

BY

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THE present report deals with further experimental investigations into the nature of the encephalitogenic factor in brain tissue responsible for the lesions of "experimental 'allergic' encephalomyelitis."

In a previous paper (Lumsden, 1949) it was shown, on the basis of over 300 guinea-pigs, that this non-transmissible encephalomyelitis can be produced regularly in severe form in over 50 per cent of animals by the repeated subcutaneous injection of sterile homologous brain tissue administered in an "adjuvant" base. The similar findings of other workers in this field were fairly fully reviewed on that occasion.

Contrary to the findings, in monkeys, of Morgan (1947) and of Kabat, Wolf and Bezer (1947), it was shown that the encephalitogenic factor is present in peripheral nerve tissue and it was considered at the time of writing the previous paper that the essential requirement for the production of the lesions with peripheral nerve tissue was to ensure that the preparation used should be of strength comparable to that of the brain tissue preparations. That this may not necessarily be the case is shown below in Experiment VI.

In this latter regard it is emphasized, as it was in the original paper, that a strictly standardized technique is called for in this work and further personal experience has shown the vital importance of carrying out these experiments on as large a scale as possible—much larger, it is submitted, than that used so far by other workers in this field. For this reason the disadvantages of using a small animal like the guinea-pig, as against the monkey, are more than compensated for by the advantages attending the use of significantly large numbers of animals. The three groups of experiments reported below have been carried out, in all, on 630 injected animals.

For one particular experiment the use of the guinea-pig presented a so-far insuperable disadvantage—namely that it was not possible to test the effect of injecting an animal's own brain tissue into itself. For this reason a trial was made of the goat. In the event of its being shown that the goat might be highly susceptible, like the guinea-pig and monkey, to this "experimental 'allergic' encephalomyelitis," it was felt that it should

be possible to remove tissue from the frontal lobe by a lobectomy sufficiently limited to avoid paralytic sequelæ, and to inject this tissue along with "adjuvants" subcutaneously into the same animal. However, of a series of eight goats repeatedly injected with goat brain two only developed neurological manifestations and these of the nature of a transient paresis only. It was considered therefore impracticable to attempt to produce ECM in goats by the injection of autogenous brain tissue. Happily this problem has been cleared up by the successful experiments along these specific lines by Kabat, Wolf and Bezer (1949) using monkeys. Despite the lack, then, of any notable results with goats in this experimental ECM work I have thought it worth while, in passing, to mention these findings.

Regarding the present experiments on guinea-pigs, these have been directed to the following ends:

(1) Comparison of the encephalitogenic activity, in guinea-pigs, of homologous brain tissue and of heterologous brain tissue from goat and human sources.

(2) Comparison of the encephalitogenic activity of human cerebral white matter and human cerebral grey matter. This was undertaken in view of the report by Morgan that, in the monkey, white matter only contains the active principle (Morgan, 1947).

(3) Confirmation of Kabat's findings that autoclaving and formalinization of the brain tissue does not destroy the encephalitogenic factor (Kabat *et al.*, 1948).

(4) Examination of the effect of guinea-pig fœtal brain with "adjuvants." This was suggested by the report of Kabat and his colleagues that fœtal rabbit brain was inactive (1947).

(5) Investigation of the effects of emulsions of skin, adrenal gland, spleen, testis and placenta and confirmatory tests with liver and kidney. The possible activity of emulsions of skin was of particular pertinence in view of the close histological similarity between this "experimental 'allergic' encephalomyelitis" and the post-exanthem encephalitides in the human subject (Lumsden, 1949).

The possibility that the encephalitogenic factor might also be present in adrenal gland was suggested by the finding (*see* Experiment VII) that the encephalitogenic factor in brain is extractable with certain of the lipoid fractions.

The possible effects of emulsions of testis and of placenta were specifically examined in view of the reports by Lewis that there exists, *in vitro*, some cross antigenicity between brain, testis, and the corpus luteum. In fact, placenta was tried entirely empirically because it was not possible to obtain the requisite amount of guinea-pig corpus luteum.

Spleen was used to see whether there might exist some interrelationship between the encephalitogenic factor of "experimental 'allergic' encephalomyelitis" and the factor concerned in the Gordon test for lymphadenoma and known to be present also in normal spleen and bone-marrow. Attempts

were indeed made to collect guinea-pig bone-marrow to test its effects when injected with "adjuvants," but, owing to an insufficient amount of the red marrow being obtained for proper standard quantitative assay, this has been suspended meanwhile.

(6) Before proceeding to attempt the isolation of the chemical fraction responsible for the "allergic" ECM it was decided to assess the importance of dosage of the brain emulsions. The results of this investigation—set out in Experiment VI below—proved rather unexpected.

(7) Attempts at chemical extraction of the encephalitogenic factor were made. These have produced some evidence to confirm the view that this factor is indeed resident in, or connected in some way with, certain lipoid fractions.

In the course of the foregoing experiments two other problems appeared. Firstly, in the animals under treatment with heterologous brain preparations there developed a splenomegaly disproportionately greater than that occurring in the animals under treatment with the other (homologous) preparations of brain and other tissues. An investigation of this splenic enlargement was therefore undertaken. Secondly, in two series of test animals—one treated with adrenal tissue and one with a cold alcoholic extract of brain—which had been reserved for several weeks well beyond the reactive period for the first assay because they had been entirely negative, a second series of injections was undertaken, this time with a potent encephalitogenic emulsion of whole brain tissue. This experiment revealed an immunity, real or apparent, in these animals. These results suggest the possibility that the "adjuvants" alone may be the responsible immunizing agency and not the animal tissue ; and they are of particular interest in view of the recent reports by Ferraro and Cazullo (1949) of the "prevention of experimental allergic encephalitis" where contrary conclusions were drawn.

General Note on Methods and Interpretation of Results

The total number of test (i.e. injected) guinea-pigs was 630. This excludes all animals used as sources of material for the actual emulsions for injection.

Throughout all the following experiments a strictly standardized routine was followed as set out in the previous paper (Lumsden 1949). All guinea-pigs, whether test or donor animals, were obtained from the same stock as used for the previous experiments. The same system of quarantine and caging was employed. All the experiments (Nos. I–VIII) set out below were performed in three groups, each group extending over a period of two to three months. No intercurrent disease occurred either amongst these test animals or amongst stock, during the whole period of the experiments (approximately nine months). The diet was the same as that given in the previous report.

The emulsions for injection were prepared according to a strictly

standardized routine as employed in the previous experiments. The standard "adjuvant" base consisted of 1 part of phenol-saline (physiological saline with 1 per cent phenol), 1 part of sterile eucerin (ungt. alcoholi:um lanæ B.P.) and 2 parts of sterile liquid paraffin containing 125 mg. of heat-killed tubercle bacilli per 100 ml. of paraffin.

Animal tissue, when used whole, was strictly 10 per cent wt/vol. of the emulsion. The organs were removed with as careful aseptic technique as possible, mushed in a sterile mortar and added to the phenol-saline in a Waring Blender. After preliminary mixing of this material the paraffin and the eucerin were added and the "homogenization" completed. Where chemically extracted fractions of brain tissue formed the ingredients of the injection emulsions, the actual weights of the fraction and of the brain tissue from which it was extracted are specified in the actual experiment. The final emulsions in all instances have been heated for one hour at 65° C. after preparation, and confirmation sterility tests have been carried out on all preparations both before and at least twice during the course of the injections. No contamination has ever been found.

Throughout the present experiments the course of injections has been a standardized one consisting of *one injection every week for five weeks*, given into the abdominal wall. The weekly dosage in all except Experiment VI was 1 ml. (± 0·05 ml.). Some animals being positive before the end of the course did not, it will be appreciated, receive the whole five injections.

As for the reading of the results of the experiments, the same strict standards of "*positivity*" have been employed: the animal has not been recorded as positive (*a*) until showing a fully established paralysis with no sign of remission, and (*b*) unless the fully developed histological picture of disseminated ECM (as reported in detail in the previous communication) was present. The insistence on complete paralysis of the hind-limbs, usually also of the back muscles, and sometimes of the fore-limbs too, *plus* the histological picture undoubtedly leads to a certain number being missed from the final roll of animals in a positive ECM series but experience now with over 1,000 guinea-pigs in this work on experimental "allergic" encephalomyelitis has convinced me that it is the safest way of recording results for comparative purposes. Cases with vague or doubtful neurological manifestations which undergo remission are no basis for definite conclusions. On the other hand, my experience has been that such rigid criteria do not prejudice the "*negative*" result; for in experimental series where frank positives have not occurred there have never been any mild or doubtful "possibles" to vitiate the issue.

Report on the Present Experiments

Experiment I.—*A comparative study of the encephalitogenic activity, in guinea-pigs, of repeated subcutaneous injections of guinea-pig, goat, and human brain along with "adjuvants."*

Twenty guinea-pigs (Nos. 151-170) were treated with a 10 per cent emulsion of fresh guinea-pig brain in standard "adjuvant" base. Of these 16 developed

encephalomyelitis at various times between the 17th and 37th days from the commencement of the course of injections. The detailed result is set out in Table I. The 4 negative survivors from this series were sacrificed on the 45th day.

Twenty-five guinea-pigs from the same stock were, at the same time as the foregoing, injected in the same way with a 10 per cent emulsion of fresh goat brain (two young adults were used). 6 developed encephalomyelitis on the days shown in Table I. The 19 negative survivors were sacrificed on the 45th day. Autopsies on the first two revealed unusually large spleens which were removed and placed in formalin without weighing. Autopsy on the third likewise showed an unusually large spleen weighing 2·30 grammes. The remainder of the series showed a degree of splenomegaly appreciably greater than observed before in guinea-pigs injected with homologous tissue *plus* "adjuvants." To confirm this quantitatively, in the subsequent series of guinea-pigs and in 100 normals used for the preparation of brain fractions and organ emulsions, the weights of each series along with the spleen weights were recorded. Attention was also paid to the possibility (a supposition sustained) that the splenomegaly was in part (not wholly) a function of the interval between the commencement of the injections and the time of sacrificing the animal. The data relating to this problem of splenomegaly are presented in the discussion.

Human brain was tested, not as a mixed emulsion of white and grey matter but, as far as possible, a separation was attempted. The detail is shown under Experiment II; but, for the moment, the interest lies in the fact that encephalomyelitis was produced by these preparations of human brain tissue in 16 out of 50 guinea-pigs so injected.

Summarizing, then, the present experiment showed that, in guinea-pigs, "allergic" encephalomyelitis can be produced by heterologous brain preparations in the same way as by homologous preparations; but that the heterologous brain tissue used (human and goat) is less efficacious than homologous. Conversely, it can be said that human and goat brain, as well as guinea-pig brain, contain the factor encephalitogenic for guinea-pigs.

EXPERIMENT II.—*Comparison of the encephalitogenic activity, in guinea-pigs, of sterile emulsions of human "white matter" and human "grey matter" with "adjuvants."*

The brain used was from a male subject, aged 58, who died suddenly of coronary infarction. There had been no clinical neurological abnormalities in the case. The brain was removed eighteen hours after death, with aseptic precautions. After stripping the pia-arachnoid and vessels, thin shavings about 2 mm. thick were peeled away from all over the convolutions, care being taken to reject fragments containing visible white matter. A sufficient quantity to make 600 ml. of a 10 per cent emulsion was readily collected. Then the cortex was removed widely to expose the centrum ovale and portions of white matter were dissected off the specimen and collected, it being found (rather contrary to expectation) more difficult to collect the requisite quantity of white than of grey matter. The final preparations were made according to the standardized technique already outlined.

Two series, each of 25 guinea-pigs, received injections of these respective emulsions. Of the 25 injected with "grey matter" 12 developed typical ECM between the 20th and 47th days. Of the 25 injected with "white matter" there were only 3 good positives, occurring, between the 41st and 51st days but one animal, notably toxic and only slightly paretic, showed scanty ECM lesions on histological examination (*see* Table I).

These findings were quite the reverse of those of Morgan (1947). This worker reported that " positive reactions occurred only in response to CNS tissue containing white matter " and she assumed that such neurological reactions as did

TABLE I.—INCIDENCE OF ENCEPHALOMYELITIS IN GUINEA-PIGS TREATED WITH BRAIN EMULSIONS. EXPERIMENTS I AND II

(The left-hand column gives the animal number; the right, the day on which positive)

Guinea-pig whole brain (*Total* = 20)		*Goat whole brain* (*Total* = 25)		*Human brain grey matter* (*Total* = 25)		*Human brain white matter* (*Total* = 25)	
No.	*Day*	*No.*	*Day*	*No.*	*Day*	*No.*	*Day*
151	17	1	25	202	20	227	41
152	23	2	25	203	20	228	43
153	26	3	27	204	20	229	47
154	26	4	30	205	23	230	51
155	28	5	35	206	25		
156	30	6	44	207	27		
157	31			208	27		
158	31			209	28		
159	31			210	30		
160	31			211	41		
161	31			212	47		
162	33			213	47		
163	33						
164	35						
165	36						
166	37						
Survivors killed on 45th day.				Survivors killed on 55th day.			

occur in 2 monkeys out of 10 so treated were due to " the estimated contamination (of the grey matter) with white matter."

Regarding the significance of these findings with white and grey matter, both in Morgan's and in the present experiments, it is doubtful if any useful conclusion can yet be drawn. Technically, the separation of grey from white matter should be simpler and more complete in the case of the human brain than in the monkey. Since the numbers of animals used here are greater than in Morgan's corresponding experiment (50 as against 20) it would seem tempting to assume that at least in the human subject the encephalitogenic factor is present in the grey matter and is absent or less concentrated in the white matter. But as Experiment VI shows, there is a real possibility of serious error in the unwarranted assumption that a quantitative difference in the incidence of ECM in two series of animals betokens a simple quantitative difference in the "concentration" of the encephalitogenic agent.

Whether, then, there is any really significantly greater encephalitogenic activity in grey than in white matter still remains to be shown. But for the moment Morgan's claim that the factor resides only in the white matter (and by inference, in the myelin), would seem to have been effectively refuted, at least in so far as it concerns the human brain.

EXPERIMENT III.—*To ascertain the effect upon the occurrence of "allergic" ECM of autoclaving and of formalinizing the constituent brain tissue of the injection emulsions.*

Twenty grammes of fresh guinea-pig brain (from the same pool as that used in Experiment I) were mixed with 50 ml. of phenol-saline and autoclaved at 20 lb. pressure for fifteen minutes. The coagulated material was allowed to cool and then homogenized with the rest (150 ml.) of the adjuvant base.

For the formalinized emulsion, the 20 grammes of fresh guinea-pig brain were mushed in a sterile mortar, 50 ml. of phenol-saline added and the whole spun in the Blender until well homogenized. To this, while spinning at high speed, 6 ml. of pure commercial formalin (40 per cent formaldehyde) were added, and then the rest of the adjuvants to 200 ml.

Both of these preparations were of a porridgy consistence, coarser than the usual white homogeneous preparations of brain tissue untreated by formalin or by autoclaving. The formalinized preparation was kept in a gas-tight container and when used emitted a powerful vapour of formaldehyde. Despite the high concentration of formalin the animals tolerated the injections well though there was a distinct tendency to necrosis at the injection sites.

In parallel with both of these preparations was run the series injected with untreated guinea-pig brain shown in Table I. It should be noted that for the normal brain as for the autoclaved and the formalinized material, the same pool of mushed guinea-pig brains was used so that these three series of experiments were strictly standardized.

The results are shown in Table II. It will be seen that 15 out of 20 were positive (histologically confirmed) by the 45th day in the autoclaved brain series as against 16 in the normal brain series up to the same day. Only 5 were positive in the same time in the formalinized brain series. The survivors in all three groups were sacrificed on the 45th day. Histologically, the latter were all confirmed as negative. The question of the time incidence of lesions has been adequately dealt with in the previous paper. From that paper it will be seen that the maximum possible expectation of positives beyond the 45th day in any of these series of 20 animals is 2; so that the results of the present experiment are, conclusively, that (1) autoclaved brain is as highly encephalitogenic as normal whole brain, and (2) formalinization of the brain tissue does not abolish its encephalitogenic activity but may reduce it appreciably.

TABLE II.—COMPARISON OF THE ENCEPHALITOGENIC ACTIVITY OF AUTOCLAVED, FORMALINIZED, AND NORMAL UNTREATED GUINEA-PIG BRAIN TISSUE.

(The left-hand column gives the animal number; the right, the day on which positive

Autoclaved		*Formalinized*		*Untreated brain*	
No.	*Day*	*No.*	*Day*	*No.*	*Day*
51	28	71	31	151	17
52	30	72	36	152	23
53	31	73	37	153	26
54	33	74	40	154	26
55	34	75	41	155	28
56	36			156	30
57	36			157	31
58	36			158	31
59	38			159	31
60	40			160	31
61	45			161	31
62	45			162	33
63	45			163	33
64	45			164	35
65	45			165	36
				166	37

EXPERIMENT IV.—*To ascertain whether the brain tissue of fœtal guinea-pigs contains the encephalitogenic factor.*

From 7 freshly killed guinea-pigs, about the 60th day of gestation, were taken 16 fœtuses, and the brains were removed under aseptic precautions, pooled, mushed,

and weighed. The usual 10 per cent emulsion with adjuvants was prepared in parallel with adult brain emulsions (in this instance actually prepared from the mothers).

The results are shown in Table III, along with those of Experiment VI. It will be seen that 15 out of 25 injected with the fœtal brain emulsion developed severe encephalomyelitis as against 17 out of 25, of the control series treated with adult brain tissue in the same dosage. The difference of 2 in 25 is certainly to be regarded as insignificant.

But one important difference was found, viz. that the positives in the fœtal brain series were distinctly earlier in appearing (*see* "Day" column in Table III); and when the incidence was graphed (fig. 1) the peak fell clearly to the left of the normal peak. This matter is dealt with more fully in the discussion.

EXPERIMENT V.—*To determine whether the encephalitogenic factor is present in guinea-pig tissues and organs other than the nervous system.*

Evidence has already been presented that the encephalitogenic factor is *not* present in liver (Lumsden, 1949), kidney (Morgan, Kabat *et al.*, Lumsden), or in muscle (previous paper). It was of manifest importance to confirm this and to extend the series of organs and tissues investigated.

For the purposes of presentation of this paper, these investigations have been grouped together as one experiment; but it has to be pointed out that in this instance these emulsions were, in fact, not tested simultaneously. Adrenal tissue was tested in the first group of experiments (Nos. 2 and 3); skin (first series), testis, and placenta along with Experiments IV and VI; and spleen, liver, kidney, and skin (Series II) along with the brain fractions in Experiment VII. It was anticipated (correctly) that these would prove negative and *would therefore act very suitably as negative controls* to each of these groups of experiments thereby ensuring —as has indeed been dealt with very fully in the previous paper (Lumsden, 1949)— that the lesion cannot be a spontaneous one in guinea-pigs and that it cannot be produced by any constituent, or combination of constituents, of the injection emulsions other than nervous tissue.

In the case of liver, kidney, spleen, adrenal gland, testis and placenta, 25 guinea-pigs in each series have been tested. In no single instance in these 150 animals has any neurological manifestation, even of the most transient nature ever been observed; and, without exception, all these brains have been examined histologically with completely negative result. The durations of these respective experiments were adrenal gland, 107; liver, kidney and spleen, 92; testis, 61; and placenta, 50 days.

As for the assay of *skin*, the difficulty of preparing a homogeneous emulsion was overcome in the following way. This assay was actually undertaken after it had been found (Experiment VII) that acetone-extracted brain is as highly encephalitogenic as—if not more so than—fresh whole brain. Since it was found impossible to grind or mince fresh moist skin satisfactorily, it was cut into tiny ribbons with scissors and these were then acetone-dried and finally kept *in vacuo* over anhydrous calcium chloride. For use, the brittle leathery fragments were milled for us (by the kindness of the Agricultural Department of the University) in a large high-speed mill specially designed for pulverizing such vegetable matter as grass, roots, etc., for the purpose of chemical assay. It may be added that a large amount of skin had to be used to obtain the 50 grammes of powder required, the loss in milling being very considerable. In this case, the shaved pelts from the thoraces and abdomens of some 18 animals were used and from these 510 grammes of fresh skin were obtained. Great care was taken to remove all traces of adherent muscular tissue from the under surface of the skin. The final desiccated skin powder was extremely light, e.g. the 21 grammes obtained in one milling occupied three-quarters of a 1-litre beaker.

Regarding the results, the possibility that skin might contain the encephalitogenic factor has not been confirmed.

However, in the first series of 25 guinea-pigs injected with this skin emulsion one animal did indeed develop a definite paralysis on the 19th to 20th day and though not completely paraplegic was sacrificed the following day for histological confirmation. Typical ECM lesions were present and a supremely important result was confidently awaited in the remainder of this series. But no further neurological (or indeed any other pathological) signs ever manifested themselves. The 24 negative survivors were finally sacrificed on the 50th day after their first injections.

No hint of any error of confusion was present, the same large common run for the whole 25 being employed throughout for this particular test. The same laboratory assistant and the same experienced animal keepers were concerned throughout.

In no other instance has a single positive result ever occurred in the 930 guinea-pigs used throughout this work. Even when working with the brain fractions (Experiment VII below) the smallest number of frank positives has been 3; and, elsewhere, even when the total number of frank positives has been small—e.g. goat brain and formalinized guinea-pig brain series—a few other animals have shown slight or transient weakness which experience has led one to suspect as a mild case of ECM though not formally admissible as such in the records.

Accordingly, it was considered that it should be accepted within the bounds of probability that this single positive skin case might either have been accidentally introduced from another cage of animals receiving brain tissue (though there was no corresponding discrepancy in the numbers); or alternatively, and more probably, that this particular animal might have received an injection of skin tissue from a syringe or needle contaminated with brain emulsion. The results of Experiment VI show that such contamination even with a minute dose—and, as has been pointed out in the previous paper, repetition of the dose is not essential—could constitute a serious fallacy. Though it has been the practice throughout to use separate syringes and needles for each different series of animals it has to be admitted that during the time of this particular experiment syringes were temporarily in short supply and the same syringe was used for two different emulsions, being washed out between the two series with boiling water and with phenol-saline. Though we were more than sceptical it had to be admitted that it was just possible that on this particular occasion the syringe used may have been carelessly washed and the animal may thus have received a small dose of brain tissue from the preceding preparation. However, there is a third possible, and more satisfactory, explanation for this solitary positive result; this we have suggested in the discussion.

In any case, *the whole experiment with skin emulsion was consequently repeated.* Another series of 25 guinea-pigs was treated with the same skin emulsion as employed for the previous experiment. It has to be noted, however, that this emulsion had been prepared eight weeks before the commencement of the present repeat experiment but in view of a previous experiment on the persistence of encephalitogenic activity in prepared brain emulsions (Lumsden, 1949) it was felt it would be most improbable that any encephalitogenic activity which a similar emulsion of skin might possess would be reduced by its conservation for eight weeks before use.

For this repeat experiment, dosage and timing was strictly standard as before. On this occasion, in no single instance did any neurological manifestations develop in any of these animals during the whole period of duration (92 days) of this particular experiment.

EXPERIMENT VI.—*To compare the effects of standard dosage* (1 *ml.*) *and of decimal dosage* (0·1 *ml.*) *of an encephalitogenic emulsion.*

This experiment was originally designed to test whether immunization could be achieved by an initial course of smaller dosage.

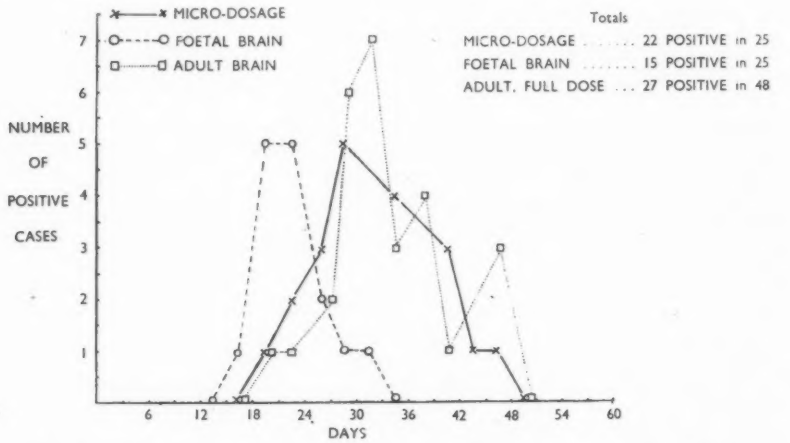
Twenty-five guinea-pigs received the usual course of weekly injections of 1 ml.

up to a total of 5 injections in still non-paralysed animals. In parallel, another 25 from the same stock received, on the same days, 0·1 ml. of the same emulsion. This dose was administered accurately from a tuberculin syringe graduated to deliver 0·01 c.c. quantities.

Of the 25 which received the full 1 ml. dosage, 17 were positive between the 27th and 47th days when the survivors were finally slaughtered. In the "micro-dosage" series 22 were positive up till the 47th day when the three "negative" survivors were slaughtered. In this instance, the positives appeared as early as the 21st and 22nd days. That is to say that one animal was positive after only 3 injections (total 0·3 ml.) ; and from Table III it will be seen that no fewer than 5 were positive after 4 injections (total = 0·4 ml.).

Whether the greater proportion of positives in the " micro-dosage " series to those in the full dosage series is significant or not it is difficult to say. It was seen, for example, in Experiment I that 16 out of 20 treated with 1 ml. doses of fresh guinea-pig brain were positive—a better result than that obtained here with the same dosage and one more comparable with the results of the "micro-dosage" series. On the other hand, the emulsion employed in the present experiment is the same in both groups and the only uncontrolled (and uncontrollable) variable here is the individual difference in the test animals. On the whole, my impression is that the difference may be significant and that further parallel experiments are called for, using on the one hand doses less than 0·1 ml. and on the other hand doses greater than 1·0 ml.

Despite the occurrence of a greater number of early positives in the "micro-dosage" series the impression that the lesions throughout this series occurred sooner than in the full-dosage is not confirmed when the results are charted on a graph (*see* fig. 1).



TIME INCIDENCE OF LESIONS COMPARED IN FOETAL BRAIN AND ADULT, FULL- & MICRO-DOSAGE. SERIES

EXPERIMENT VII.—*Assay of the encephalitogenic activity, in guinea-pigs, of homologous brain tissue treated with various solvents and of various lipoid fractions.* (*"Adjuvant" technique throughout.*)

The following methods were employed:

(*a*) Cold alcohol extraction, with encephalitogenic assay of both the extract and the residue.

TABLE III.—INCIDENCE OF "ALLERGIC" ECM IN GUINEA-PIGS TREATED WITH ADULT AND FŒTAL GUINEA-PIG BRAIN IN 1 ML. DOSES AND WITH ADULT GUINEA-PIG BRAIN IN 0·1 ML. DOSES

(Experiments IV and VI)

Adult guinea-pig 1·0 *ml. dose*		*Fœtal guinea-pig* 1·0 *ml. dose*		*Adult guinea-pig* 0·1 *ml. dose*	
No.	*Day*	*No.*	*Day*	*No.*	*Day*
350	27	250	19	375	21
351	27	251	19	376	22
352	28	252	20	377	23
353	30	253	21	378	25
354	30	254	21	379	27
355	30	255	21	380	27
356	31	256	22	381	28
357	31	257	22	382	29
358	33	258	23	383	30
359	33	259	23	384	30
360	33	260	24	385	30
361	34	261	25	386	31
362	36	262	26	387	33
363	36	263	28	388	34
364	38	264	33	389	34
365	38			390	36
366	47			391	36
				392	40
				393	41
				394	41
				395	43
				396	47

(Survivors in all above groups killed on 47th day)

(*b*) Acetone extraction, with assay of the acetone-extracted residue only.

(*c*) Extraction of *cerebrosides* with boiling absolute alcohol, and assay both of this cerebroside fraction and of the brain residue minus cerebrosides.

(*d*) Encephalitogenic assay of a crude *sphingomyelin* + *cerebrosides* mixture extracted according to the method of Carter, Haines, Ledyard and Norris (1947).

(*e*) Encephalitogenic assay of a crude *lecithin* + *cephalin* mixture, obtained by drying *in vacuo* the ether filtrate obtained in (*d*).

Extraction procedures for (*a*) and (*b*) :

(*a*) Cold alcohol treatment : 39 grammes of fresh guinea-pig brain were extracted for three days at room temperature (18–20° C.) with 3 daily changes of absolute alcohol and filtered through a No. 1 Whatman filter paper. The residue was dried *in vacuo* over anhydrous calcium chloride. 4·87 grammes of this residue were collected and blended with 200 ml. of adjuvants. The final product was therefore approx. 2·5 per cent of desiccated alcohol-extracted residue and equivalent to a 20 per cent emulsion of brain tissue.

The alcoholic filtrate was evaporated *in vacuo*. This final extract was of butter-like consistence and weighed 3 grammes approx. This, too, was made up to 200 ml. with standard "adjuvant" mixture.

(*b*) Acetone treatment : Another 39 grammes of fresh guinea-pig brain tissue were extracted with daily changes of acetone for three days at room temperature. After filtration, the residue was evaporated *in vacuo* and desiccated over calcium

chloride. The final material weighed 7·5 grammes and was made up to 200 ml. with adjuvants. The filtrate was, as a result of a technical accident, grossly contaminated by a reflux of tap water during evacuation and was consequently rejected.

Results of (*a*) *and* (*b*).—Of 20 guinea-pigs in each of these series (*see* Table IV), 17 of those injected with the acetone residue and 7 of those injected with the alcohol residue developed gross neurological signs and the histological lesions of typical disseminated encephalomyelitis. The negative survivors were sacrificed on the 45th day. Amongst those injected with the alcohol extracts there was not a single positive at any time during the whole period of 107 days during which they were under observation until the further series of injections given to these animals for Experiment VIII below were started.

Extraction procedures for (*c*), (*d*), and (*e*) :

It having been confirmed that treatment of brain tissue with alcohol and acetone did not destroy, or even reduce appreciably, its activity, an encephalitogenic assay of the individual lipoid fractions became a feasible programme.

(*c*) Extraction of cerebrosides : The brains of 50 normal adult guinea-pigs (half of them male and half female), all removed within an hour of killing, were pooled and mushed in a sterile mortar, just over 250 grammes of brain tissue being collected. The viscous brain pulp, moistened with a little absolute alcohol, was homogenized in the Waring Blender, then washed with abs. alc. into a 2-litre flask. One litre of absolute alcohol was added and the whole brought to, and maintained at, the boil over a water bath. After extraction thus for forty-five minutes the contents of the flask were filtered through No. 1 Whatman filter paper in a glass filter funnel held in a copper jacket filled with water maintained at the boil by a gauze-protected Bunsen flame. The residue was washed back into another flask, re-extracted with absolute alcohol as before for forty-five minutes and filtered. These two filtrates were mixed. At first clear, they rapidly precipitated a dense homogeneous cloudy precipitate. After cooling on ice this was filtered, washed with cold alcohol, again and finally dried gently over a water bath at 65° C. This dried precipitate was then washed with about 100 ml. of chloroform but the resultant mixture proved partially unfiltrable, even *in vacuo*, having an almost jel-like nature. Accordingly, the rest of the chloroform was evaporated off on the water bath at 65° C. This dried product of (crude) cerebrosides extracted from 250 grammes of brain tissue weighed 5·5 grammes and was of a character not unlike pale beeswax. It was made up to 200 ml. with adjuvants.

The residue of brain tissue after removal of the cerebrosides was likewise made up as a 10 per cent emulsion with adjuvants.

(*d*) Extraction of *sphingomyelin + cerebrosides* and of *lecithin + cephalin* fractions : The brains of another 50 normal guinea-pigs were similarly removed, just over 250 grammes being collected. The pooled brains were pulped in a mortar with a few millilitres of acetone and finally homogenized in the Blender. The material was then washed into a flask with acetone and another 500 ml. of acetone added. This was allowed to extract at room temperature for forty-eight hours, then filtered. This extraction was repeated six times over a period of ten days. The earlier *extracts* deposited abundant cholesterol crystals on keeping. The *residue* was treated five times with 250 ml. quantities of B.D.H. sodium-dried ether, each extraction (twenty-four to forty-eight hours) being carried out in sealed bottles. The pooled filtrates were evaporated *in vacuo* till only 200 ml. remained and the final drying was done over a water bath at 55° C. The final product was a darkish saffron, buttery material—LECITHIN + CEPHALIN — weighing 3·95 grammes ; it was made up to 200 ml. with adjuvants. The ether-extracted residue contained the crude SPHINGOMYELIN + CEREBROSIDES mixture and after drying out was made up to a 10 per cent emulsion with adjuvants.

Results.—When tested out for encephalitogenic activity on groups of 25 guinea-pigs each these yielded the results shown in Table IV. It will be seen that the

preparations of "brain minus cerebrosides" proved equally potent to the control normal brain tissue tested in parallel with these groups, 10 being positive in each. Three in the "cerebrosides" and four in the "sphingomyelin + cerebrosides" groups gave frank positive results and there were one or two possible mild cases with transient weakness. In the "lecithin + cephalin" series all the animals without exception remained completely negative during the whole ninety-two days of the experiment.

Regarding the interpretation of these findings it is manifestly premature at this stage to incriminate any specific chemical compound in the brain but the following conclusions would seem at least to be legitimate :

(1) The encephalitogenic factor is not destroyed by treatment with acetone, alcohol (hot or cold), ether, or chloroform.

(2) It is extractible along with certain of the complex cerebral lipoid fractions but not with the simple lipoids soluble in cold alcohol.

(3) It is not removed with the ether-soluble phosphatides.

Whether the factor might be sphingomyelin or a cerebroside it is not possible to say from these data for it will be seen that, by the methods employed, the "cerebrosides" fraction probably contains an appreciable amount of sphingomyelin and that the "sphingomyelin" fraction undoubtedly does contain cerebrosides. In view of what has been said in Experiment VI on the efficacy of "microdosage," even a gross quantitative difference between the true sphingomyelin and cerebroside content of the respective mixtures would not necessarily be reflected in the number of positive guinea-pigs injected with the emulsions concerned.

EXPERIMENT VIII.—*The effect of injections of homologous brain tissue plus "Adjuvants," in guinea-pigs previously treated with "adjuvants" along with* (a) *adrenal tissue,* (b) *an alcoholic extract of brain.*

Two series of guinea-pigs (each of 25), one previously treated with the cold alcoholic extract of brain (Experiment VII) and the other with the emulsion of adrenal gland and "adjuvants" (Experiment V), having both yielded completely negative results, were kept alive beyond the usual period of the experiment just to obviate the remote possibility of unusually late reactors. None such occurring, the idea presented itself of testing upon them the effects of the ordinary "positive-control" emulsions (of guinea-pig brain tissue plus "adjuvants") from a subsequent experiment. The results were sufficiently striking to justify reporting them here. They seem to suggest that the mere injection of "adjuvants" alone may in some way produce immunity to the encephalitogenic factor in brain tissue.

Method : One series of 20 guinea-pigs had received a full course of 5 weekly injections of 1 ml. of a 10 per cent homologous adrenal emulsion in the standard "adjuvant" base, commencing on 22.2.49. The other series of 20 guinea-pigs had received likewise a full course of 5 weekly injections of the cold alcohol extract of homologous brain in "adjuvants" commencing 21.2.49. On 8.6.49—107 days later —a course of injections with fresh 10 per cent guinea-pig whole brain in "adjuvants" was started and 5 weekly injections given.

Results : One positive only occurred—on the 29th day—in the series previously treated with the alcoholic extract of brain. That the brain emulsion was a potent one was shown by the results of the control group of 25 where 10 frank positives occurred by the 50th day (*see* Table IV).

DISCUSSION

Short commentaries on the interpretation and significance of the individual experiments have already been made under the respective descriptions. Discussion here will therefore be limited to a few aspects

of special importance which may have some bearing on the nature of the encephalitogenic agent and its mode of action.

TABLE IV.—ENCEPHALITOGENIC ASSAYS, ON GUINEA-PIGS, OF CERTAIN LIPOID FRACTIONS AND RESIDUES OF HOMOLOGOUS BRAIN TISSUE

("ADJUVANT" TECHNIQUE)

POSITIVES (*First Series*)

Whole brain control (20)		*Acetone extracted residue* (20)		*Alcohol extracted residue* (20)		*Alcoholic extract* (20)	
No.	*Day*	*No.*	*Day*	*No.*	*Day*	*No.*	*Day*
151	17	131	20	91	22	None positive	
152	23	132	23	92	22		
153	26	133	26	93	23		
154	26	134	26	94	25		
155	28	135	26	95	25		
156	30	136	28	96	25		
157	31	137	28	97	34		
158	31	138	28				
159	31	139	28				
160	31	140	28				
161	31	141	31				
162	33	142	31				
163	33	143	33				
164	35	144	36				
165	36	145	36				
166	37	146	36				
		147	38				
Total duration = 45 days only						Total duration = 107 days	

POSITIVES (*Second Series*)

Whole brain control (25)		*Brain minus cerebrosides* (25)		*Cerebrosides* (25)		*Sphingomyelin + cerebrosides* (25)	
No.	*Day*	*No.*	*Day*	*No.*	*Day*	*No.*	*Day*
401	23	425	19	450	23	475	32
402	27	427	23	451	25	476	39
403	28	428	24	452	33	477	42
404	30	429	26			478	50
405	32	430	26				
406	36	431	27				
407	36	432	27	Lecithin + Cephalin			
408	39	433	39	None positive			
409	45	434	40				
410	45	435	50				
Total duration = 50 days				Total duration = 92 days.			

The Nature of the Encephalitogenic Agent

Several reasons were presented in the previous paper (Lumsden 1949) against the view that the encephalitogenic factor might be a living agent. The fact, confirmed here in Experiment III, that it is not destroyed by thorough autoclaving or even by presentation in a strong concentration of formalin, surely disposes of that possibility. By the same token, it seems improbable too that the agent could be an enzyme.

The idea that the encephalomyelitis may be due to a latent virus infection already resident within the animals, and reactivated in some way by the chemical agency of the material injected, is surely also untenable in view of the fairly extensive data now presented. Throughout the whole of these experiments involving close on 1,000 guinea-pigs the encephalomyelitis has been strictly limited to those receiving injections of brain or peripheral nerve material with "adjuvants." No other combination of animal tissue with "adjuvants" has ever produced the lesion. Likewise, were it a latent virus infection whose stimulation into activity were dependent on the circulation within the animal's blood-stream of some chemical substance derived from dead brain tissue then, surely, injections of sterile brain tissue alone—without "adjuvants" —would be just as efficacious as the combination. This is not the case. It is true, as has been fully discussed in the previous paper, that brain tissue alone can produce the lesion in animals but this is an infrequent and capricious result and in that case usually requires extremely prolonged administration.

The encephalitogenic factor is apparently limited to brain and peripheral nerve. Its presence has not been demonstrated in skeletal muscle, in liver, kidney, spleen, adrenal gland, testis or placenta. In view of the histological similarity of this experimental lesion to post-exanthem encephalitis in Man, there was an attractive possibility that skin might be encephalitogenic under the experimental conditions used for the assay of brain. The evidence presented in Experiment V seems to show, however, that skin does not contain the factor though it is true that one animal in the first series of 25 did indeed yield a positive result. We have tried in the commentary to that experiment to argue that this single positive result should be discounted but perhaps a dour verdict of "non-proven" would have been more scientific! One is tempted to wonder whether a small fragment of cutaneous nerve, imperfectly disintegrated by the Blender, could have been injected and in itself been large enough to liberate the factor.

As for the location of the agent within the brain tissue from which it is derived, the results of Experiment II suggest that at least in the case of cerebrum it is not evenly distributed in the white and in the grey matter. But the present findings with the guinea-pig have been the reverse of those of Morgan with the monkey and show that any inference that the encephalitogenic factor is limited to the myelin sheath is quite premature.

One of the most striking findings in this work so far published is that of Kabat and his co-workers relating to the appearance of encephalitogenic activity in fœtal monkey brain at the same time as myelinogenesis. In Experiment IV here a similar attempt was made with fœtal guinea-pig brain. With nearly full-term guinea-pig fœtuses the brains showed high encephalitogenic activity but not appreciably higher than that of the brain tissue from the parents. There was, however, one difference between the two groups which, if confirmed, may have considerable significance—namely that the positives in the series treated with fœtal brain occurred in an average distinctly sooner, the peak falling ten days ahead of that for the normal incidence of lesions (fig. 1). Though it cannot be said that there was any qualitative difference in the severity of the encephalitic reaction between the two groups, this finding may reflect not so much an *earlier* onset of the lesion in the fœtal brain series, but a *more rapid evolution*. It will be remembered that with the system of accountancy employed throughout the present experiments, positives are recorded at their maximal periods of intensity and not at the times of onset. Consequently, though the total number of positives in the two groups is virtually the same this by no means denies the possibility (indeed probability) in these experiments of a significantly greater encephalitogenic activity in the fœtal brain series. Unfortunately, it has not been possible so far to carry out, on guinea-pigs, any more extensive experiment along these lines to find out at what stage in brain development the encephalitogenic activity is acquired as this would involve large-scale breeding and maintenance of numbers beyond our present capacity. This particular problem is obviously one to which the small animal is unsuited.

Finally, with regard to the chemical nature of the encephalitogenic factor, our findings have been discussed fairly fully at the conclusion of Experiment VII.

Mode of Action of the Encephalitogenic Agent

Some speculations as to the mode of action have already been made in the previous paper and present remarks will therefore be limited to special points which have arisen since the time of writing that paper.

Firstly, there is the significance of dosage dealt with in Experiment VI. Clearly the agent is of potent character for, it was seen, as small a dose as 0·03 gramme of brain tissue injected into an adult guinea-pig of over 500 grammes can produce severe disseminated encephalomyelitis. Presumably there is a minimal limit since that irremovable amount of peripheral nerve tissue (whether somatic or visceral) present in muscle, skin, liver, kidney, testis, etc., does not produce the lesion. Whether there is a maximal limit still remains to be determined. There is always the possibility that a large depot of injected brain material may "deflect" the antigen—a conjecture which formed the basis of Ferraro and Cazullo's experiment on the "prevention" of the lesion. If indeed such "deflection" does occur our difficulties on the interpretation of experimental

findings in this work are going to be increased enormously for it will mean, for instance, that the optimal dosage of any brain fraction will have to be ascertained before the activity of one fraction can be compared with that of another.

Secondly, another feature of the mode of action bears emphasis; namely, that the development of the lesions does not necessarily depend on repetition of the injections. Reference has already been made to this when the role of allergy was discussed in the previous paper.

Thirdly, an important feature has become evident only by frequent repetition of these experiments and it is one for which adequate allowance has certainly not been made by authors on this subject, viz. that there may be a fairly wide variation in the incidence of lesions from experiment to experiment even with a standardized emulsion of normal adult guinea-pig brain with "adjuvant." Throughout each group of experiments proceeding simultaneously, a positive control group injected with normal adult guinea-pig brain in "adjuvants" has always been employed and a brief review of the tables both in the present and in the previous paper will show that the incidence has varied from over 80 per cent to, on one occasion, exactly 40 per cent within the fifty days of the experiment in this case. In summarizing the findings in the previous paper it was stated that this encephalomyelitis "can be produced regularly in over 50 per cent of guinea-pigs, etc." but it will be appreciated that in more than one instance only three or four animals out of a group of 25 have not shown the gross manifestations which have been insisted upon as the criteria of positivity. In such high-incidence groups it is possible that even the few negative survivors have had a milder transient form of the same reaction which has been missed; and therefore, far from being a fortuitous phenomenon, this "experimental 'allergic' encephalomyelitis" reaction expresses some fundamental law or principle.

Fourthly, though the evidence so far available points to the agent being some specific chemical substance—not, in my opinion, necessarily implying any allergic mechanism—it seems probable that when administered with "adjuvants" it becomes antigenic and is capable of conferring immunity (Ferraro and Cazullo, 1949; Lumsden, 1949). That this antigenicity depends upon some conjugation mechanism is suggested by the results of Experiment VIII.

Fifthly, the enlargement of the spleens, reflecting as it presumably does a generalized reticulo-endothelial hyperplasia, has proved an interesting line of investigation.

For the purpose of comparison it is evidently essential, except for the controls, to standardize the time factor—i.e. the time interval between the onset of the injections and the time of killing when the spleen was weighed. This has been rendered easy by the fact that in these later experiments the time of killing off the negative survivors (except in special groups such as the second skin series and the groups for Experiment VIII) has been standardized at the 45th to 50th day. Accordingly,

in the case of series injected with brain tissue, the weights of the spleens of the survivors have been directly compared with each other and with those from animals treated with tissues other than brain. The data for the normal controls are from the 100 animals sacrificed to obtain brain tissue for the lipoid fractions. The results are shown in Table V.

TABLE V.—ANALYSIS OF BODY-WEIGHT/SPLEEN-WEIGHT RATIOS IN GUINEA-PIGS RECEIVING FULL COURSES OF INJECTIONS WITH TEST EMULSIONS, COMPARED WITH NORMAL CONTROLS

(*Note.*—The figures for injected series relate only to negative survivors killed between the 45th and 50th days)

Group	*Total number*	*Sex*	*Average body wt. (grammes)*	*Average spleen wt. (grammes)*	*Ratios (to unity)*
Normal	50	F	710	0·81	878
Normal	25	F	758	0·71	1073
Normal (starved 36 hours)	25	M	709	0·98	726
Homologous Brain (full dosage) (Series I and II) ..	18	M	518	0·72	720
Homologous brain (full dosage) (Series III and IV) ..	21	13 M, 8 F	601	0·99	607
Homologous brain (micro-dose)	3	M	547	0·85	644
Homologous placenta ..	23	F	611	0·92	665
Homologous skin (Series I)	22	F	641	1·00	641
Heterologous brain (human) (grey matter + white)	29	M	561	1·18	475
Heterologous brain (goat)	17	M	583	1·32	440

That this separation of positive ECM cases from negatives in the various series injected with brain tissue is essential is evident from the data shown in Table VI which gives, in this instance, the individual figures as well as the averages to show the relationship of spleen weight increase to the time increment.

From the data in Tables V and VI it will be evident that in these animals :

(1) The spleen weight rises in all animals irrespective of the nature of the injection material, till the 50th day and possibly later.

(2) This increase in spleen weight occurs independently of the occurrence of encephalomyelitis ; and,

(3) Is independent of the nature of the component tissue in the injection emulsion whether it be brain, placenta, or skin.

(4) This rise in spleen weight is significantly greater in animals injected with heterologous brain than with homologous.

There remains one final consideration to be discussed—as to the relationship, if any, of this experimental lesion and the neuropathy

TABLE VI.—THE RELATIONSHIP OF SPLENOMEGALY TO THE TIME FACTOR

(Body weight and spleen weight in guinea-pigs injected with homologous and with heterologous brain tissue)

Homologous								*Heterologous*			
Full dosage (Series IV)				*Micro-dosage*				*Human grey matter*			
Positives			*Negatives*			*Positives*		*Negatives*		*Positives*		*Negatives*	
Day	*B.W.*	*S.W.*	*Day*	*B.W.*	*S.W.*	*Day*	*B.W.*	*Day*	*B.W.*	*Day*	*B.W.*	*Day*	*B.W.*
24	740	0·70	53	630	1·10	21	460	0·60	47	570	0·90	20	690	0·95	55	510	0·75
28	640	0·70	53	730	1·22	22	440	0·70	47	630	0·92	20	750	0·65	55	600	1·17
29	570	0·65	53	550	1·11	23	550	0·70	47	440	0·72	23	480	0·60	55	545	0·72
31	528	0·85	53	510	1·20	25	523	0·65				25	503	0·70	55	650	1·00
33	550	0·82	53	490	0·51	27	450	0·60				27	750	1·30	55	510	0·80
37	475	0·81	53	510	0·92	27	370	0·40				27	552	1·07	55	512	0·95
37	660	0·75	53	570	1·10	28	420	0·65				28	470	0·85	55	567	0·88
40	500	0·65	53	480	1·10	29	642	1·02				30	466	0·65	55	517	1·20
46	672	1·05	53	605	1·15	30	400	0·54				41	616	0·23	55	655	2·10
46	410	0·59	53	680	1·20	30	380	0·45				47	370	0·63	55	490	1·30
			53	610	1·10	30	476	0·57							55	585	0·95
			53	485	0·90	31	510	0·82							55	870	1·57
			53	535	0·82	33	527	0·90									
						34	560	0·90									
						34	537	0·62									
						36	474	0·67									
						36	570	0·77									
						40	535	0·65									
						41	450	0·50									
						41	467	0·60									
						43	480	0·46									
						47	395	0·53									
Averages																	
	574	0·76		568	1·03		483	0·65		547	0·85		565	0·76		584	1·12
Ratios (to unity)		755			551			743			644			743			521

occurring in positive Gordon tests for lymphadenoma and capable of production in the guinea-pig, as in the rabbit, by intracerebral inoculation. The question is of special moment since there is a good deal of evidence that the neurotoxic agent in the Gordon test is of non-living nature (Steiner). There are, however, wide biological differences. Firstly, there is the difference of the route of inoculation—only intracerebral inoculation being efficacious in the Gordon test. Then there is the wide difference in the time incidence—the lesion developing in the Gordon test within twenty-four to forty-eight hours. Then there is the distinct difference in the histological picture, for whereas in this experimental "allergic' 'ECM there is a marked perivascular lymphocytic and microglial reaction disseminated throughout the CNS, in the brain in positive Gordon tests the only histological change appreciable is the loss of Purkinje cells in the cerebellum. These differences would seem to be fundamental but this neuropathy does indeed provide an interesting and problematical parallel with "experimental 'allergic' encephalomyelitis."

Summary and Conclusions

(1) Further to the previous report on the encephalitogenic activity, in guinea-pigs, of sterile homologous brain emulsions injected subcutaneously in a standard "adjuvant" base, it is confirmed that human and goat brain will likewise produce this "allergic" encephalomyelitis in guinea-pigs. These heterologous emulsions are, however, less highly encephalitogenic than homologous brain tissue.

(2) In guinea-pigs injected with heterologous brain there results a greater splenomegaly than in animals injected with homologous brain. This splenomegaly is independent of the "allergic" ECM, occurring equally in encephalitic and non-encephalitic animals, and it is maximal at a much later period than the maximal period of incidence of the encephalitis. Homologous tissue from organs other than brain produces a degree of splenic enlargement equal to that caused by homologous brain. Heterologous tissue other than brain has not been tested.

This reaction on the part of the spleen, being independent of the encephalitogenic effect, is a further support of the contention made in the previous paper that several independent types of reaction can and do occur in animals injected with brain tissue and "adjuvants."

(3) Some preliminary evidence is given to suggest that "allergic" ECM can be produced in goats, but results are much poorer than in guinea-pigs and monkeys.

(4) Human cerebral grey matter was more highly encephalitogenic for guinea-pigs than human white matter. This is contrary to the findings of Morgan in monkeys who considered that the encephalitogenic factor was limited to the white matter, and, by inference, to the myelin.

(5) Autoclaving and formalinizing of guinea-pig brain tissue does not destroy its encephalitogenic activity. This is confirmatory of the findings of Kabat, Wolf and Bezer with brain tissue of monkeys.

(6) Brain tissue from nearly full-term guinea-pig fœtuses is highly encephalitogenic, and alone of all brain tissues or extracts tested produces its peak response some ten days sooner than adult brain tissue. Whether this is simply an expression of a quantitatively greater encephalitogenic activity rather than a qualitative difference has not been definitely established.

(7) It is shown that liver, kidney, muscle, spleen, adrenal gland, testis and placenta are entirely without encephalitogenic effect in guinea-pigs. Acetone-dried skin is likewise apparently devoid of the factor.

(8) It has been emphasized throughout the present as well as the previous experiments that a completely standardized technique has been employed as regards dosage, etc. Evidence is now presented that much smaller dosage of brain tissue is still as highly encephalitogenic : a total of 0·03 gramme of brain tissue will produce disseminated encephalomyelitis in full-grown guinea-pigs of 500 grammes or more. The minimal and (if any) maximal doses have not yet been determined.

(9) The encephalitogenic factor in guinea-pig brain tissue is not destroyed by treatment with acetone, alcohol, ether or chloroform (nor by keeping—*see* previous report). The brain residues after acetone extraction are as potent as, if not more so than, the parent whole brain. The encephalitogenic factor is extractable along with sphingomyelin and the cerebrosides but not at all with lecithin and cephalin.

(10) Evidence is presented to suggest that injections of "adjuvants" with tissue other than brain and with non-encephalitogenic alcohol extracts of brain, will immunize guinea-pigs against "allergic" encephalomyelitis. It is inferred that the essential immunizing factor is therefore resident in the "adjuvants" alone and it is suggested that, contrary to their interpretation, the immunity findings reported by Ferraro and Cazullo are due to this cause.

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THE PHENOMENON OF TACTILE INATTENTION WITH SPECIAL REFERENCE TO PARIETAL LESIONS

BY

MACDONALD CRITCHLEY

TACTILE inattention refers to that phenomenon whereby a patient who has no profound loss of sensibility, nevertheless fails to perceive a tactile sensation on one side when bilaterally simultaneously stimulated. Thus when the patient, with his eyes closed, is touched with a wisp of cotton-wool or with the point of a pin, upon the back of the hand or the cheek, he perceives the contact and says so. But if touched with two pieces of cotton-wool or two pins upon both hands or sides of the face, he then declares that he can feel only one stimulus.

This phenomenon, it is suggested, may be demonstrated quite often if specially looked for. It is by no means rare with lesions of the cerebral hemisphere and in particular when the lesion lies within the parietal lobe.

The question of nomenclature is a peculiarly difficult one and is discussed more fully later in this paper. "Tactile extinction" is the term which is perhaps most commonly employed in this connexion, though for many reasons unsuitable. While it is true that no term has yet been suggested which is entirely appropriate, "inattention" is perhaps the least objectionable. Throughout this communication the phenomenon will be spoken of as "tactile inattention," and it will be regarded as synonymous with the "tactile extinction" of Bender and his co-workers.

HISTORY

H. Oppenheim (1885) seems to have been first to describe the particular clinical method of testing disorders of sensibility which is the subject of this present communication. He narrated four case-histories to illustrate this technique. The first concerned a woman of 74 years with a right hemiplegia. Although there was no sign of sensory loss, when pin-pricks were simultaneously applied to corresponding places in both upper limbs, she felt them only over the left side. The same held true when the legs were simultaneously touched with the point of a pin; less constantly did it apply to the face. "Double stimulation"—as Oppenheim called it—gave a similar result when a cold object was used instead of a pin. His second case was also that of a right hemiplegia in a woman of 45 years, but there was some reduction in superficial pain sensibility as well. With bilateral simultaneous testing pin-pricks were felt only on

the left side even though the right side may have received a much stronger stimulus. An analogous phenomenon could also be demonstrated in the auditory sphere. Thus, whereas a watch could be heard ticking in either ear alone, only on the left side was the sound heard when watches were held at a similar distance from both ears simultaneously. Oppenheim's third patient was an alcoholic of 54 years who developed a left-sided hypæsthesia and hypalgesia, with simultaneous stimulation of both hands, the patient perceived the pain only on the right side, unless the stimulus was very intense, in which case the pain reached awareness from both sides simultaneously. The author's last case concerned a man of 40 years with a weakness of the right leg. In this case again, bilaterally applied pain stimuli to the legs were felt on the left side only. Oppenheim made an additional observation of interest, namely that if the pain stimuli were applied to the legs not quite simultaneously, then the patient would experience two distinct sensations.

Oppenheim's paper did not attract much attention, and even though the author referred again to the phenomenon of " doppelte Erreizung " in his textbook (1900) and in all subsequent editions and translations, we do not find any comparable cases in the literature for some years.

E. Jones (1907) had noted incidentally, while studying the problem of allochiria, that in one of his patients, bilateral touches simultaneously applied were felt over the left side only. The author did not embark upon any discussion of this point, however, nor did he refer to Oppenheim's earlier observation.

The next contribution was by O. Maas (1910) who studied a case of left-sided apraxia using Oppenheim's method of double stimulation. Although there was said to be no difference between the feeling of superficial contacts over the two sides, bilateral stimulation at symmetrical points produced awareness of contacts only over the right side. This was so, even when the right side was touched lightly at the same time as the left side was jabbed with a pin : only the touches on the right side were felt. Double stimulation with hot and cold objects gave similar results.

The following year saw a brief reference by H. Head and G. Holmes (1911) in their studies on cortical disorders of sensibility to instances where the appreciation of weights held in the two hands at the same time was affected in an unexpected fashion . . . . " A weight is placed in each hand and allowed to remain there. From time to time the patient is asked to estimate the relation between the two weights. He will almost certainly say the one in the normal hand is heavier ; *but gradually he begins to think that there is no weight in the abnormal hand*, and the sensations produced by its removal may even be mistaken for the reapplication of the weight to the hand. He says, ' You have put the weight on again.' . . ."[1] Unfortunately the authors did not discuss these findings

[1] Italics are not in the original.

which include, for the first time, mention of the duration of the stimulus in the production of unilateral ignoral, or non-awareness of stimuli.

We find no further reference in the literature to a phenomenon of this order for the next twenty years, until we come to an extraordinary case-record made by H. Pinéas (1931). This author's case concerned a patient (whom I also had the opportunity of examining) with a left-sided imperception of extra-personal space, ignoral of the left arm and leg, a difficulty in dressing, a Gerstmann's syndrome, palipraxia, a tendency to the execution of contrary actions (the " Penelope phenomenon "), and an alloæsthesia. From a study of this paper, it appears that unilateral sensory contacts were well appreciated on both sides, but that when stereognosis was tested in both hands together, the object in the right hand only was recognized. (". . . So ist es verständlich dass sie, obwohl die Stereognosie beiderseits völlig intakt ist, nur *den* Gegenstand bemerkt, den sie in der rechten Hand hält, nicht aber den *gleichzeitig* in der linken Hand befindlichen.") Pinéas' paper was a purely clinical one, but in a personal communication (1932) the author kindly informed me that the patient died the following year. Autopsy revealed two softenings within the right hemisphere, one in the parietal area and another on the convex surface of the occipital lobe.

The same patient had been described by P. Schuster (1931) at a meeting of the Berliner Gesellschaft für Psychiatrie und Neurologie. Regarding the sensory disturbances Schuster said that the patient, holding an object in each hand and with the eyelids closed, would at once recognize what was in the right hand. She would become aware of what lay in the left hand only after a delay, or after the object had been removed from the right hand. (". . . Gibt man der Kranken in jede Hand einen Gegenstand, so erkennt sie (bei Augenschluss) den rechten sofort. Den in der linken Hand befindlichen brachtet sie erst dann, und erkannt ihn (trotz Augenschlusses) auch dann, wenn man ihr den Gegenstand aus der rechten Hand herausgenommen hat.") The same patient also showed an alloæsthesia in that pain and touch stimuli applied to the left hand were often referred to a corresponding point on the right hand.

The story of double simultaneous tactile stimulation needs to be interrupted at this point to refer back to the work of W. Poppelreuter (1917) who, using the technique of simultaneous testing, drew attention to a similar phenomenon in the optic sphere which he termed a " hemianopic weakness of attention," or more briefly, "visual inattention." Here the patient, though able to detect an object shown at the periphery of either visual field, seemed to be able to identify it on one side only when objects were presented simultaneously to the left and to the right. This phenomenon attracted much more notice than Oppenheim's observations, and similar case-reports quickly followed at the hands of such authors as G. Holmes (1918, 1919), K. Goldstein (1918), H. Head (1926), G. Riddoch (1935), A. J. Akelaitis (1942) and others. In a more recent

study by F. Thiébaut and L. Guillaumat (1945) this phenomenon was spoken of as a " hémianopsie rélative."

A considerable revival in interest in the practice of double tactile stimulation has taken place within the last four years, probably as the result of the writings of M. B. Bender upon this subject. It has now become, in certain neurological centres at any rate, a routine test in cases with cerebral lesions.

M. B. Bender and L. T. Furlow (1945) recorded a case of visual inattention, or as they termed it—" visual extinction in homonymous fields " —as the result of a left-sided parieto-occipital injury. In this case-report they mentioned quite briefly in a footnote that there was a decrease of cutaneous sensory perception on the right side when the left hand was stimulated simultaneously ("cutaneous sensory extinction phenomenon").

M. B. Bender (1945) studied a number of patients with cutaneous sensory disturbances due to lesions at various levels of the neuraxis, in order to determine the " nature and degree of sensory dulling or extinction " using Oppenheim's technique of double stimulation. The author found that " sensory extinction " (as he called it) occurred in certain patients with lesions of the parietal cortex. Unilateral "obscuration " or " abolition " of sensation was most striking when bilateral graphæsthetic stimulation was employed. Bender drew attention in this paper to a number of other sensory phenomena which will not be discussed here in detail such as alterations in the sensory adaptation time, and the aggravation or precipitation of unilateral pain by contralateral cutaneous stimulation.

The following year P. W. Nathan (1946) reported a case of a war injury to the right parietal area which was followed by various defects, including disorders of spatial recognition, of calculation, of topographical sense, of visual orientation, and of dressing. There was a tendency towards neglect of the left side of the body, and a left-sided visual " inattention." The left limbs were slightly weak, with an extensor plantar response : there was also a left-sided hypæsthesia. Over the left side of the body a well-marked " extinction " phenomenon could be demonstrated. Nathan gave the credit for this method of bilateral simultaneous testing to Head and Holmes, seemingly unaware of the earlier papers by Oppenheim and Maas. Nathan's discussion brought out some interesting ideas. He rejected the hypothesis that suppression of function might be a general law for the entire cerebrum ; he suggested, however, that it might prove to be a characteristic of the parieto-occipital and occipital cortices. The two cases known to Nathan (his own and Bender's) were instances of lesions of different sides of the brain, suggesting that suppression was not a prerogative of the dominant hemisphere. He asked himself whether suppression was dependent or not upon the coexistence of unawareness of the affected limb. Finally he mentioned the importance of a qualitative study of this phenomenon to find out

whether one type of stimulus could suppress another type, and if so, whether it would be possible to determine a " hierarchy of sensory stimuli to the cortex."

N. Reider (1946) also described the same phenomenon, which, however, he preferred to call " sensory suppression." Two cases were recorded in some detail. The author agreed with Bender and Furlow in thinking that the phenomenon could not be explained wholly upon the basis of an inattention. Judging from the cases so far reported, Reider inculpated the parietal lobe.

M. B. Bender and H. L. Teuber (1946; 1948) returned to the question of " extinction " but more particularly as it applied to the visual sphere.

G. Vercelli (1947) also referred to a number of cases of " sensory eclipse " as shown by bilateral simultaneous tactile testing after unilateral cerebral lesions. He considered that the parietal lobe was usually, though not exclusively, the region involved. This author too did not believe that lack of attention was the cause of the phenomenon.

M. B. Bender and S. B. Wortis (1947) discussed at the American Neurological Association a patient whom they later described more fully. In this case there occurred both alloæsthesia and cutaneous extinction. Occasionally, when simultaneously and bilaterally stimulated, the patient felt both stimuli, but referred them both to the left, i.e. less affected side. In the succeeding discussion, K. Goldstein associated the defects with a general incapacity to react to two separate stimuli at once.

S. J. Ross and G. Fountain (1948) made a rather detailed study of a case of tactile " extinction " in a man who had a partial surgical excision of the right fronto-parieto-temporal cortex. There was a left-sided sensory impairment, associated with extinction phenomena, for such sensory modalities as pain, touch, temperature, and weights. This phenomenon also held true for simultaneous stimulations with dissimilar contacts. It is to be noted that this patient exhibited a certain neglect, ignoral, or unawareness of the left half of the body. Auditory extinction was tested for but could not be demonstrated. Visual extinction could not be investigated owing to the patient's severe visual defect.

M. B. Bender, S. B. Wortis and J. Cramer (1948) studied a woman believed to be suffering from Alzheimer's disease, and who showed—among many other anomalies—slight right-sided sensory disturbances. The patient exhibited a consistent " preference " for the left side both as regards perceptual reactions and motor performance. The latter was shown in the greater use of the limbs of the left side and a tendency to turn to the left. Perceptual preferences were betrayed by extinction phenomena for cutaneous, kinæsthetic, and also visual and auditory stimuli. Alloæsthesia also occurred at times, in that she was apt to refer a stimulus object located on the right side, to the left. This dislocation applied to objects seen, heard or felt. The patient subsequently died and was found to have well-marked cerebral atrophy, especially of the parietal regions.

S. B. Wortis, M. B. Bender and H. L. Teuber (1948) contributed a paper on the theoretical problems raised by the phenomenon of extinction generally; other questions also arose which will be discussed later in this paper. These authors referred to a point previously mentioned in one of Bender's earliest papers, namely that extinction may also occur after spinal lesions, though more frequent after cerebral affections.

M. B. Bender (1948) gave a short account of the advantages of the method of simultaneous bilateral sensory testing in routine neurological examination. Illustrative case reports were briefly given, and in this paper Bender for the first time quoted the original study on the subject made by Oppenheim sixty-three years previously.

Clinical Manifestations of Tactile Inattention

Since the practice of double sensory stimulation has become habitual in the neurological examination of patients with cerebral lesions, a number of instances of tactile inattention have been found. The general features noted originally by Oppenheim have been confirmed, but various clinical points arise for more detailed discussion.

Favourable and unfavourable stimuli.—Tactile inattention was originally noted when painful stimulation was employed, and this is perhaps the readiest method of quickly demonstrating the phenomenon. But other modalities of sensation, including light touch and temperature, may be effective in this connexion. In one blind patient indeed, this phenomenon could be demonstrated by as massive a stimulus as that of grasping first her one hand, releasing it, and then grasping her other. These actions on the examiner's part were recognized by the patient, but when both of her hands were simultaneously clutched by the examiner, she said that only her right hand was being held. Bender has stated that bilateral vibrating tuning forks fail to show extinction, even though contacts with cotton-wool, pin-prick, or hot and cold test-tubes are effectual. This failure on the part of vibratory sensation is not always the case however, for in my experience it may also form part of the general picture of tactile inattention, in the same way as light touch, pain, and so on. Possibly, as Bender asserted, complex stimuli, involving spatial and temporal qualities, are more readily extinguished than are simple punctate contacts of short duration, especially when heavily charged with feeling-tone. Thus extinction of weights, or the recognition of the size, shape, consistency and identity of objects held in the hands, may betray in a striking fashion a different perceptual reaction on the two sides. A coin placed in each hand separately may be promptly recognized. When two identical coins are placed in the hands simultaneously, the article may be recognized at once on the "normal" side. On the "abnormal" side the patient may not seem to realize the presence of any object at all, or he may only after a delay become aware of its existence. He may not, however, recognize its nature though able slowly

to describe its shape and size. Or he may realize that each hand holds a coin but in the affected hand the coin may be incorrectly named—being regarded as either bigger (or smaller), heavier (or lighter) than expected.

Bender was of the opinion that bilateral graphæsthesia was of particular value in demonstrating tactile inattention though it is not clear exactly what technique he used. After apparently inscribing upon the two palms incongruous figures or letters, doubt was engendered in the patient's mind as to the nature of the stimulus upon his affected side. But this test is one of particular difficulty, and may prove impossible in the case of normal persons.

Ross and Fountain found that when their patient immersed his hands in a bowl of hot or of cold water, he felt correctly the stimuli on both sides even though tactile inattention was otherwise demonstrable. The authors suggested that the feeling of " wetness " accounted for the ability to perceive double stimuli. No explanation was offered however as to why wetness alone should be able to break through the barrier of tactile inattention. The true explanation may be entirely different, as will be mentioned later.

Stimuli of equal and unequal intensity.—It is usual to employ bilateral stimulation of similar nature and equal intensity in testing for tactile inattention. Bender, indeed, in his first paper on the subject, used great care to ensure that the stimuli should be of equal strength and he employed graduated algesiometers for this purpose. Such precautions are not necessary, for when tactile inattention is well-marked, even powerful pin-pricks are inhibited by faint stimuli applied to the normal side. This observation was actually made in the earliest papers by Oppenheim and by Maas. Nevertheless this is not always so, for when tactile inattention is less conspicuous, a sharper stimulus on the unaffected side may have the effect of overcoming a weaker stimulus on the other. Extinction (or distraction) by reason of a stronger stimulus is more frequent and more striking in the visual sphere. Thus visual inattention is most marked when a stimulus object of greater size and brightness is displayed in the normal visual field, as if the degree of visual inattention were proportional to the optical significance of the rival stimulus.

The role of continued stimuli in tactile inattention.—When rubbing or scratching contacts are made on both sides, tactile inattention may be well demonstrated. If then the stimulus is withdrawn from the normal side the patient will now probably feel the continuing stimulus on the other, until such time as the scratching or rubbing is resumed on the normal side.

Tactile inattention is well shown by continued painful pressure with the point of a pin ; when the pressure is withdrawn from the normal side the pain may now be felt at once on the affected side. In my experience, however, the patient usually does not feel the pain on the affected side when the pin is taken away from the normal limb—as if the extinc-

tion effect outlasted the duration of the suppressing factor. But if a third pin-prick is made on the affected side quite near the point of continued pressure of the pin, the fresh incoming stimulus is at once felt. It may be concluded therefrom that a permanent hypalgesia of the affected limb is not the explanation of the phenomena. Indeed, even a light touch with a piece of cotton-wool alongside the " extinguished " pin-prick may be appreciated immediately. In other cases again, after the painful pressure has been removed from the healthy side, the patient may—*only after a delay of up to half a minute*—feel the pin-prick which is still being continuously applied to the abnormal side. This phenomenon is rare and may be the result of an inadvertent intensification of pin-prick stimulus on the examiner's part.

Dissimilar tactile stimuli.—Tactile inattention may be demonstrated, not only when identical modes of sensation are employed, but also when the stimulation differs in quality on the two sides of the body. Thus cotton-wool drawn across the healthy limb may successfully suppress the pain of a pin-prick applied to the abnormal side. This observation was first made by Maas.

One patient in our series showed, as the result of an embolism of the left middle cerebral artery, a right-sided impairment of sensibility. Cold contacts were interpreted as being hot, but when tested with bilateral stimulation (pin-prick on the right, cold test-tube on the left) he either ignored the cold contact altogether or else regarded it as an indifferent stimulus, devoid of thermal properties.

Of considerable interest is the possible efficacy of auditory or visual stimuli in extinguishing or suppressing a purely tactile stimulus on the affected side. Writing in 1948, Wortis, Bender and Teuber said they had not so far seen a case where visual stimuli succeeded in extinguishing a tactile stimulus. Such, however, has been found in at least one patient in our series. Moreover, in a few patients, the appreciation of a pin-prick over the affected side—previously intact—was " suppressed " when an auditory stimulus was sounded in the opposite ear.

These cases of auditivo-pain, or visuo-pain " extinction " must be regarded as very rare.

Synchronous and asynchronous stimulation.—Ordinarily tactile inattention results from bilateral stimuli applied strictly at the same time. When, however, an interval of time separates the two contacts, extinction may not occur *provided that the interval between the two contacts is long enough.* Thus, if the stimulus is applied to the abnormal side just before the rival stimulus to the normal side, then the contacts are felt as two ; but if the procedure is reversed, suppression or extinction may occur provided that an interval of no longer than three seconds separates the two contacts.

Symmetrically and asymmetrically placed stimuli.—It is usual to demonstrate tactile inattention by means of contacts applied to mirror-

opposite sides of the body, e.g. both cheeks, both hands, both sides of the trunk. There is abundant evidence, however, that the two stimuli need not be symmetrically placed, and that, for example, a feeling of pain, a stimulus to the affected hand, may be " suppressed " by a rival stimulus applied to the opposite forearm, trunk, or even the side of the face.

Ipsilateral " extinction " phenomenon.—It is important to realize that two contacts applied to the affected side may, at times, be felt as one, and not as two. This is quite independent of the phenomenon of defective tactile discrimination as demonstrated by the compass test, a phenomenon which may well co-exist in these cases of cerebral disorders of sensation. The two ipsilateral stimuli may be separated in space as far as the face from the hand, or the arm from the leg. When " extinction " occurs in such cases, it is the distal portions of the limbs which suffer most. For example a stimulus to the back of the hand may be extinguished by a stimulus applied to the cheek or forehead ; or a stimulus to the face, arm, hand, or trunk, may extinguish a stimulus simultaneously affecting the foot.

A similar phenomenon is known in cases of visual inattention where a stimulus in, say, the lower quadrant, may suppress the perception of a stimulus in the upper, both, however, being situated on the same side of the mid-line.

Incomplete forms of tactile inattention.—The problem of extinction is more complex than a mere presence or absence of a sensory experience. As the result of a stimulus applied to the healthy side the stimulus on the abnormal side may be felt very imperfectly, or only after a delay ; or the sensation may be very incorrectly localized. In other words, " degrees of extinction " can occur—if one may use such a contradiction in terminology. According to Bender, these may vary from a slight reduction in sensory adaptation time, or rise in the sensory threshold, with dulling of the pain sense, to complete extinction of sensibility.

In the patient already quoted who felt cold contacts as hot over the left side of the body, this illusory perception was considerably modified when bilateral stimuli were employed. When two cold test-tubes were simultaneously applied to the two sides, the contacts on the right side were either ignored altogether, or else they were recognized as of indeterminate character. The coldness was no longer felt as " hot ".

As previously stated, these incomplete forms of extinction are best identified in the case of stereognosis. A similar object dropped into the two hands may be appreciated and named on the normal side, while on the other side there may occur any one of the following reactions :

(1) It may be completely ignored.
(2) Its presence may be denied.
(3) It may be felt, but its physical properties imperfectly described.
(4) Its physical properties may be well described, but its identity not recognized.

(5) It may be recognized, and named, but only after a delay.

(6) It may be named, but the patient may assert that it differs in size or weight from the object held in the normal hand.

The mental state of the patients.—Both tactile and visual inattention can occur in patients with a clear sensorium and with no obvious intellectual deterioration. But in so much as all these patients possess a cerebral defect, some degree of organic psychical change is to be expected. In many cases, however, this is so subtle as to require special methods of psychometry for its elicitation. On the other hand, tactile inattention often accompanies states in which the sensorium is clouded, amounting to great lethargy and imperfect contact with the environment. It is interesting to surmise whether such a perceptual phenomenon as tactile inattention can be said ever to occur in the unconscious state; if so, the term "inattention" would be inappropriate. Obviously the patient's insight and interpretation will not be available in such cases. So long as unconsciousness is not too deep, the phenomenon of extinction can be looked for, and perhaps demonstrated, by noting the automatic movements of withdrawal when a limb is jabbed firmly with a pin. If we were to find withdrawal movements of each limb in turn when vigorously stimulated, but if when both limbs were similarly treated only one limb moved, then a tactile "extinction" can be surmised. There is, of course, a source of error in this technique, for the withdrawal movement may not have been a pseudovolitional gesture of protest but a purely reflex phenomenon. Bender has quoted a case where double stimulation with a pin had produced bilateral "reflex" withdrawal of the hand, but the patient—whose consciousness was not too much obnubilated—denied having felt the stimulus on one side.

So far, however, tactile inattention (or extinction) has not been reported in a deeply unconscious subject.

Can tactile inattention occur with intact sensibility?—In some of the earliest cases described, double stimulation is said to have evoked tactile inattention from segments of the body where no sensory loss could be found. Since these pioneer records, the cases reported have mostly shown obvious, albeit minor, sensory disturbances. It is tempting to assert that where "no sensory loss" has been reported, finer and subtler forms of impairment were probably overlooked. While in some cases a hemihypæsthesia and a hemihypalgesia were noted, other cases showed merely impaired discrimination (shown by compass tests), defective localization of contacts, imperfect stereognosis and disordered postural sensibility. Blunting to light touch and to pin-prick is often to be found, not over one-half of the body but only over the hand and foot of the affected side, and perhaps even only a portion of the hand or foot.

At the same time tactile inattention obviously cannot be demonstrated when there exists a profound sensory loss. The clinical phenomenon of tactile inattention may thus appear during a phase of transition in

the case of a cerebral tumour, being demonstrable neither in the very early, nor in the very late, stages.

"*Extinction of tactile inattention.*"—In a number of personal cases a rather unusual phenomenon has been observed. Double stimulation has demonstrated in the ordinary way a tactile inattention. With repeated testing, this may be broken down. Or if a very strong stimulus succeeds in producing a sensation on the affected side; or if a painful stimulus is maintained in the form of a continued pressure with the point of a pin, the patient may eventually become aware of stimulation over those parts of the body where previously there had been extinction. Thereafter, and for some time, repeated testing in the ordinary way with double stimulation fails to reveal tactile inattention. In such a case it would seem as though the tactile "extinction" had itself become temporarily extinguished. The intervention of attention on the part of the patient seems to be indubitable in such cases, even though its mode of operation may be less obvious.

Tactile inattention and cerebral dominance.—It can be asserted straightway that tactile inattention can be found over either side of the body, independently of the handedness of the patient. In other words it does not depend upon whether the diseased hemisphere happens to be the dominant or the subordinate half of the cerebrum. None the less, there is perhaps a slighter tendency for the minor or subordinate hemisphere to be associated with the phenomenon of tactile inattention. As will be seen, this in turn depends upon the coexistence—which sometimes obtains—of a unilateral disorder of the body scheme.

Imperception of one half of the body.—In the case report described by Pinéas and by Schuster, the most striking feature was an unawareness of the left half of the body, though appropriate close testing showed that no gross motor or sensory loss was present. Here too were evidences of alloæsthesia and of tactile inattention. The latter was not specifically looked for, except in the test for bilateral synchronous stereognosis. How many other recorded cases of tactile inattention have also shown this hemi-somatic imperception cannot be said, and it seems clear that this point was not considered, or specifically tested for, in many cases. Maas' patient may well have been a case in point. Nathan's patient had many parietal defects, including a "tendency towards neglect of the left side of the body." In the case published by Ross and Fountain it was stated that ". . . in response to commands, he would ignore the left side of the body. When told to extend his arms, he would invariably extend only the right arm. On the second command to extend both arms, he would then bring up his left arm. When told to flex his knees, he would flex only his right knee." Again, in the patient with bi-parietal cortical atrophy described by Bender, Wortis and Cramer, there was a preferred use of the limbs on the left side with a liability to turn to the left. Here again alloæsthesia from the left to the right was found, for visual and auditory as well as tactile stimuli.

It is probably safe to suggest that if all patients with imperception for one body-half were to be subjected to appropriate testing, a tactile inattention would also be found. The converse does not necessarilly hold, however, for in many cases where tactile inattention is demonstrable, a gross imperception for the corresponding side of the body cannot be found.

After parietal lesions, however, minor degrees of hemisomatic imperception are probably by no means uncommon, though rarely identified. This may show itself by such features as a lack of spontaneity in voluntary movement, and a greater reluctance to use the affected hand during bimanual activities than the degree of paresis or sensory loss would warrant. A tendency for the patient to drop objects out of the hand, and a subjective description of " heaviness " of the affected limb, are probably also evidence of a partial neglect of one side.

Association with Alloæsthesia.—Reference has already been made to the not infrequent association of tactile inattention with alloæsthesia. The argument might perhaps be adduced that tactile inattention is, indeed, nothing but an alloæsthesia, whereby all cutaneous stimuli applied to the abnormal side are appreciated but are incorrectly referred to a mirror-opposite point on the other side. But tactile inattention can occur without alloæsthesia. When the two phenomenon occur together the tactile inattention may be obscured. It is possible that the literature holds a number of instances where alloæsthesia has proved the most striking phenomenon and tactile inattention has either been overshadowed or—more probably—never specifically tested. In the semiconscious patient recorded by J. Zutt (1931) there was a hemianopia, visual and spatial disorientation, apraxia, agraphia, and a dressing disability. When sensory tests were applied he said that all the touches were on the right side, though he demonstrated correctly the point stimulated. Whether this is an instance of alloæsthesia, or of right-left disorientation is not clear from the record.

Alloæsthesia of cerebral origin entails a rivalry between stimuli arising from areas of differing perceptual thresholds, coupled with either a right-left orientation, or else an imperception for one side of the body. Such are also the circumstances which strongly favour the appearance of a tactile inattention.

The factor of attention.—As originally asseverated by Poppelreuter, the unawareness of stimuli coming in from one side during bilateral stimulation, may ostensibly be explained as being due to neglect of—i.e. inattention towards—objects on that side. Hence the terms visual and tactile inattention. Bender was perhaps the first author to question such an explanation. He emphasized that the act of focusing the patient's attention on the affected side " did not appreciably influence the extinction or obscuration phenomenon." This observation has been supported by Vercelli, and others, but it is doubtful whether the question has been

closed by the demonstration that volitional consciousness is without effect upon tactile " extinction."

In our experience patients have varied in their response to this instruction. If told during the test to " focus their attention " upon the segment that is being stimulated (or is about to be stimulated) the patient may continue to neglect the stimuli, as stated by Bender *et al.* This, indeed, is the common event ; but it is not always the case. Some patients when so directed, may after a while declare . . . " Now I feel something on my other hand as well ! " Patients vary considerably in this respect, not only from one day to another in the same patient, or even from moment to moment. Yet another type of response when the patient is directed to focus his stream of consciousness on to the limb stimulated by a continued pin-prick, is for the stimulus to be felt only at the moment when the pin is withdrawn.

Should the patient be questioned as to his subjective sensation during these sensory tests, he may state—as did one of Bender's patients—that . . . " the stronger sensation distracted him from his ability to perceive sensation on the opposite side." When one of my patients was asked how he accounted for his failure to recognize bilateral stimuli, he explained it by saying . . . " I keep forgetting." One of Bender's patients (a spinal case) used the words . . . " It seems as if I don't pay attention to my left side when both sides are being stimulated." Another of my patients showed a partial tactile inattention when a pear was placed in each hand. He recognized the object quickly on the one side but slowly on the other. He then went on to say . . . " I knew all along there was something there, but I don't seem to bother about that hand, somehow."

Morbid Anatomical Considerations

In the great majority of cases tactile inattention occurs as a manifestation of a cerebral lesion. Bender, it is true, has reported its occurrence in some spinal affections. His Case 3 (1945) was that of a Brown-Séquard syndrome due to a gunshot wound of the right side of the cord at the level of C.6. Double stimulation with pin-prick showed that the painful sensation over the left buttock was dulled or abolished as soon as a stimulus was applied to the right buttock. The extinction phenomenon went even further. Pain in the left sacral dermatomes was abolished by a simultaneous stimulus over the opposite side of the neck, and to a lesser extent also by a pin-prick applied ipsilaterally over the face and upper part of the trunk.

As regards peripheral nerve and spinal root lesions Bender wrote that none of these patients showed the complete extinction phenomenon.

Tactile inattention is most often and most characteristically displayed with cerebral lesions, and in the great majority of cases, the lesion has lain within the parietal lobe. Sometimes the pathological process has been extensive and can only be described in such terms as fronto-parietal,

temporo-parietal, or occipito-parietal. In Ross and Fountain's case, a large glioblastoma was found at operation deep in the right temporal lobe. To remove this growth *in toto* a partial excision of the fronto-parieto-occipital cortex was performed. In most recorded cases the parietal lesion was probably deep in its extension. Whether tactile inattention can occur with a purely cortical affection of the parietal lobe is uncertain. It is of course arguable that a "purely cortical" lesion is probably a hypothetical conception which rarely, if ever, occurs in life. Certainly tactile inattention can occur with such a pathology as a parasagittal meningioma which merely rests upon the parietal lobe, compressing it no doubt but not invading it. Again, tactile inattention has been well demonstrated in cases of cortical atrophy most marked in the parietal area; but there too the white matter also becomes involved, as shown by shrinkage and by internal hydrocephalus.

If, then, tactile inattention is to be regarded as a common manifestation of parietal disease, the question may at once be raised: how would this phenomenon show itself in cases of bilateral parietal lesions? Possibly the picture would be one of an ignoral of all tactile stimuli without, however, any actual loss of sensation. This paradoxical state of affairs wherein there is an indifference towards tactile contacts without any demonstrable analgesia, becomes striking when the stimuli are of a potentially painful character, e.g. deep pin-pricks, or extreme thermal contacts. The important clinical point will be whether or not the eyes are open; when the patient watches the examiner apply the contacts he will doubtless state that he feels them: with the eyes closed he will show indifference.

This hypothetical syndrome of "bilateral tactile inattention" is of course reminiscent of what P. Schilder and E. Stengel (1928, 1930) have already described in another setting, under the term "asymboly for pain." Here the patients appear indifferent towards painful stimuli although no analgesia can be demonstrated. The authors believed that in such cases there was an inability to project accurately painful percepts on to the body image.

There is yet another way in which bilateral tactile inattention might show itself clinically. When bilaterally stimulated the patient might respond to the contact on one side only, but the side in question would vary from one moment to another. This phenomenon has been well seen in a case of Anton's syndrome (of cortical blindness with lack of insight and with confabulation). Such a case is of additional importance, in that it illustrates (1) that tactile inattention may occasionally occur with cerebral lesions outside the parietal lobe; and (2) that the factor of inattention is perhaps more important than the presence of reduced cutaneous sensibility. We must admit therefore that tactile inattention may occur at times with cerebral lesions outside of the parietal lobe. In such cases a considerable degree of intellectual confusion is to be expected.

There is very little information regarding the occurrence of tactile inattention in association with areas of hysterical anæsthesia. In one case only was this phenomenon demonstrated in a patient with a mild right-sided hypæsthesia which was in part, if not wholly, hysterical in character. Here an organic substratum probably existed. At a later date the sensory loss deepened so as to become a complete hemianæsthesia. When this stage had developed the tactile inattention could no longer be evoked.

Terminology

When first described by Oppenheim no special term was applied to this phenomenon as revealed by the technique of double stimulation. Maas also contented himself with a simple description of the facts as he observed them. When something comparable was found in the visual sphere, Poppelreuter spoke of a visual inattention. The natural outcome would, therefore, be the use of the expression " tactile inattention." Right from the first, however, Bender objected to the use of the term " inattention " in these connexions and laid stress upon the fact that perception remained in abeyance, in the case of both touch and vision, even though the patient's attention may have been expressly directed to the segment of the body, or the half of the visual field, as the case may be. In other words the factor of " attention " need not play an important role. In his early papers, Bender spoke of "visual obscuration and extinction," and of " sensory dulling or extinction," respectively. Later he shortened these phases to visual and tactile extinction.

Reider preferred to speak of a " tactile suppression." all the more so because he was tempted to correlate the phenomenon with the suppressor bands of the cerebral cortex. He, too, agreed with Bender and his colleagues, that the factor of "attention" is not all-important. Vercelli, on the other hand, spoke of "sensory eclipse" in this connexion. "Tactile ineffectiveness " would perhaps be the apposite term if Goldstein's viewpoint is to be followed strictly.

None of these terms can be regarded as satisfactory. Tactile inattention has the merit of being clear, almost self-explanatory ; it suggests a purely passive manifestation of sensibility, though of course it may be inaccurate in doing so. As quite rightly pointed out, a deliberate attempt at focusing the attention may not necessarily ablate the phenomenon. Nevertheless, it is likely that in most instances deficiency in attention is conspicuous, and may play the responsible role.

The terms " extinction," " suppression," and " eclipse " possess two other great disadvantages. In the first place, they suggest an active process influencing the cerebral mechanism of perception, and we may be wrong in assuming any such active role. Secondly, all three terms connote a certain totality : an annihilation or obliteration of sensation which is not always the case. Thus at times double stimulation merely

causes a reduction in sensation, or a delay in appreciation, or a defect in recognition on the affected side, phenomena which cannot well be regarded as examples of an extinction, suppression, or eclipse. Tactile " suppression " has the added drawback of suggesting that suppressor bands play a part here—an assumption which is probably quite unjustified. Even the word " extinction " can be challenged for similar reasons in that it has already been taken into the nomenclature of neurophysiology, in an utterly different connexion.

Less objection can be raised against the expression " tactile repression " in that it readily embraces examples of incomplete extinction as well as complete. There is a disadvantage in using a word which psychologists already employ in a different connexion but this practice is a common weakness in neurological terminology.

On the whole it is considered that tactile " inattention " is the term open to the least criticism.

The Nature of Tactile Inattention

It becomes a matter of discussion whether tactile inattention can be adequately explained along physiological lines, or whether it is necessary to have recourse to a psychological viewpoint. Some observers have been tempted to regard tactile inattention as a straightforward phenomenon capable of explanation by the use of purely physiological conceptions. A process of " blocking " of sensory impulses has been visualized, resulting from the intervention of synchronous pre-potent impulses from the other, i.e. normal, side of the body. The clinical phenomenology nevertheless argues powerfully against any such mechanistic idea. Tactile extinction is often a variable phenomenon, capable of demonstration one moment and not the next. Under repeated testing : with very forceful stimuli : under the influence of visual gaze, the phenomenon of tactile inattention may break down, and thereafter repeated tests may show and " extinction of tactile extinction " as we might call it. Such manifestations cannot possibly be interpreted along any but psychological lines.

In this latter connexion we are faced with the problem of the mutual effect of multiple painful stimuli in more normal individuals. Since Hippocrates wrote that " of simultaneous pains in two places the lesser is obliterated by the greater," we have the so-called Heymans' law of inhibition that simultaneous stimuli " mask " each other (1927). An application of these ideas can be witnessed in the widespread use of counter-irritation for the relief of pain. K. Duncker (1937) has been able to demonstrate experimentally that the intensity of a passive pain stimulus is reduced when an active-painful stimulus is applied to another part of the body. It was found that only the *pain* component of the first stimulus was lessened when a second stimulus was applied, the *pressure* component continuing unchanged. A strident raucous noise moreover was just as effective as a second pain stimulus. The original pain could also be relieved by an active willed muscular contraction, as everyone

knows from common experience. In the case of tactile inattention, however, especially as encountered in parietal lesions, the important factor would seem to be not so much the occurrence of two synchronous pain stimuli, as the operation of bilateral stimuli which need not be painful at all. Lhermitte and de Ajuriaguerra (1942) have referred to ". . . la loi générale des sensibilités symétriques, toute excitation forte portée sur le territoire sain supprime les sensations attenuées dont est le siège le secteur lésé." Two points are emphasized in this statement, namely the symmetry of the foci stimulated, and inequality of the threshold of sensation at the two sides. A rivalry is envisaged between competing mirror-opposite stimuli of unequal intensity, whereby the weaker perceptions become suppressed.

This conception although plausible fails to account for all the clinical evidence. In the first place the stimuli concerned need not be of a painful nature, for the " extinction " phenomenon can usually be readily demonstrated for every modality of tactile sensation, as also at times for auditory sensation, and for visual impulses. Secondly the stimuli need not necessarily be symmetrically placed and a stimulus on, say, the healthy cheek, may cause a stimulus applied to the affected hand to be extinguished. Thirdly, it is possible that inequality of the intensity of the stimulus may not be essential, for a weak stimulus may at times suppress a strong one. Inequality in the intensity of the percept may possibly, however, be an essential condition, though there is not yet enough data to be dogmatic upon this point.

Bender originally sought to explain the data along physiological lines, and he drew attention to the evidence pointing to the bilateral connexions of each sensory cortex with the periphery. Dusser de Barenne demonstrated in certain lower mammals that strychninization of the sensory cortex on one side will be followed by a bilateral hyperalgesia. Foix (1922) emphasized, under the term " anæstho-agnosia," the existence of bilateral sensory impairment following unilateral parietal lesions. Of greater relevance was Bender's clinical observation that a spontaneous unilateral pain can be intensified by contralateral tactile stimulation—apparently in defiance of the axioms of Hippocrates and of Heymans. Thus the pain of a causalgic limb may be increased, according to Bender, if a series of painful pin-pricks are applied to the opposite extremity. Bender sees in this so-called " tactile intensification " an excitatory phase of a process of which tactile extinction constitutes the negative phase. The interaction, he believes, take place in the cerebral cortex, where there may be a bilateral functional relationship between sensations streaming in from the two sides of the body.

The most convincing explanation of tactile extinction in cerebral lesions would be to regard the problem as one of rivalry between two contending stimuli, transcending what occurs in the normal experimental subject. A stimulus applied to a bodily segment of high perceptual threshold fails to attain conscious level as it is distracted bya rival stimulus

synchronously applied to a segment with a lower perceptual limen. This distraction takes place even if the force of the stimulus to the affected side is great, and even when the two rival stimuli concern different sense modalities. In some cases indeed, a tactile impulse may be distracted by a visual or an acoustic stimulus ; in such it is difficult if not impossible to imagine any physiological or psychological explanation other than that of attention. It is essential, however, that the two stimuli should be simultaneous in application, though not necessarily equal in duration. Thus bilateral pin-pricks are felt as two if the contact is not made synchronously. If the two pressures with a pin are maintained, and the distracting stimulus is then removed, the " extinguished " pain stimulus remains in abeyance for a matter of seconds. This theory of a rivalry between contending impulses emphasizes the role of the parietal lobe in the development of the body scheme. It is not surprising that tactile inattention should so often occur in those cases where the body image suffers most, i.e. where hemisomatagnosia, or imperception of one body-half, occurs.

This hypothesis of a distracting influence upon rival stimuli is in reality a return to the conception whereby inattention is looked upon as the responsible defect. Tactile extinction thus becomes once again tactile inattention. The brain injured individual cannot " attend " to two simultaneous claimant stimuli, to the detriment of the one which is of lesser intensity, or which proceeds from a segment of higher limen, or from regions which have become less obtrusive within the body-scheme.

Bender, Reider, Vercelli, and others, have claimed that this hypothesis of inattention is untenable. Their main argument centres round the observation that tactile extinction continues even after the patient has been instructed to focus his attention upon the affected limb. The authors have not discussed the problem more deeply and are content to dismiss the hypothesis on the basis of the clinical observation quoted.

It is submitted that the problem is far more difficult, and that " inattention " cannot be discarded out of hand merely upon the grounds that expectancy does not necessarily modify the extinction phenomenon. " Attention " is a psychological mechanism of considerable complexity, and the active focusing of what James called " expectant attention " on to a particular and localized segment is a process quite different from the more passive reception of incoming percepts. This act of directed expectancy, or "pre-perception" as Lewes called it, is a difficult procedure ; difficult in that it cannot be maintained for longer than a few moments, and difficult in that it cannot be focused upon minimal stimuli without considerable fluctuations. It is highly probable that in the case of the patient with a parietal lesion, expectant attention cannot successfully be directed to the opposite half of the body. Thus, when such a patient is directed to " focus his attention " upon the affected limb, the result may be quite inadequate, and insufficient to upset the clinical phenomenon

of tactile " extinction." As James pointed out, attention to an object cannot take place until the appropriate cortical centre is excited ideationally as well as sensorially. In the case of parietal lobe lesions, these circumstances may never be achieved.

That this is the case is supported by the observation that tactile extinction is, as a rule, immediately ablated when the patient opens his eyes and watches, i.e. attends visually to what is going on. Thus a patient with a parietal lesion may display tactile inattention in the ordinary way when his two hands are simultaneously pricked with a pin. Even when he is told (while his eyelids are closed) to concentrate his " attention " upon the affected hand, he still may not feel the pin-prick on double stimulation. But as soon as his eyelids open and he witnesses the test as it is being performed, he at once admits that he actually feels as well as sees the pin on both sides. This fact argues strongly in favour of inattention being responsible for the original extinction phenomenon.

This clinical observation is, it is submitted, all important. The fact that tactile " extinction " breaks down the moment the patient opens his eyes and attends to what is happening can scarcely be explained on any basis other than that of attention. It probably also explains why this phenomenon of tactile inattention cannot be demonstrated with bilateral immersion of the hands in water. The reason lies not so much in some innate property of "wetness"—as Ross and Fountain suggested—but in the humdrum circumstances of the test. The production of the bowl of water—or the positioning of the patient before the wash-basin—will conduce to a state of expectancy. Finally, the immersion of one or both hands into the water would naturally be carried out with the eyes open, and therefore would invalidate the test.

Any co-operative and intelligent patient who has been displaying tactile inattention in the ordinary way usually expresses astonishment as soon as his eyes are opened and the nature of the test is revealed to him. When asked to comment upon the effect of vision on the perception of two simultaneous stimuli, one patient remarked ". . . When my eyes are closed the pin-pricks upon my good side seem to be sharper than when my eyes are open." In other words, the contrast between the two thresholds is enhanced when visual attention does not assist, and the distracting power of the major stimulus becomes intensified.

The importance of distraction of attention is shown by still other observations. Thus, the fact that tactile inattention can occur as an ipsilateral manifestation, argues straightway against any simple physiological explanation inculpating suppressor bands, or a bilateral cortical representation of each body-half. When, on the affected side, a stimulus to the proximal part of a limb " extinguishes " a simultaneously applied distal stimulus, we probably are witnessing the same interplay of rival stimuli arising from two zones of differing sensory thresholds, so that the impulses coming from the area with the lower threshold (i.e. the proximal part of the limb) dominates attention. It is of interest to discuss in what

way this simultaneous, double, ipsilateral stimulation differs from the compass test. As Head and Holmes first clearly showed, the power of recognizing "two-ness" is a separate function which may be destroyed by a cortical lesion. The compass test applied in cases of parietal disease differs in three main respects from the phenomenon of ipsilateral tactile inattention : (1) the two contacts are widely separated in the case of tactile inattention (arm to hand ; thigh to foot ; or even face to hand). (2) The two contacts in the case of the compass test are applied to an area of uniform perceptual threshold ; but with tests for tactile inattention, the two stimuli are applied to areas of differing perceptual significance. (3) The lack of feeling of " two-ness " with the compass test is associated with an impaired accuracy of localization, and the contact of " one-ness " is referred to a region midway between the two points actually stimulated. With the test for ipsilateral tactile inattention, the solitary stimulus appreciated is referred not to an intermediate locus but more or less accurately to the site of the stimulus lying within the area of lower perceptual threshold.

Bender (1946) himself has referred to other disorders in tactile perception which may follow parietal lesions and which may accompany what he calls tactile extinction. Thus sensory " adaptation time " may be altered, being usually shortened, though occasionally prolonged. Though Bender does not say so, this phenomenon in itself can best be equated with disordered attention. This is well illustrated by one of his patients who advanced the following plausible, if naïve, explanation of an embarrassing situation. ". . . I was sitting in the parlor with my right hand around my girl. Her mother was sitting opposite us. Suddenly I noticed a change in the mother's facial expression. She seemed uneasy and disturbed by something. So did my girl. When I looked to the right, I found that my right hand had dropped down to the girl's breast. I quickly straightened out and apologized. At the same time, I could not understand how it happened that I was not aware of my hand. Since then I have tested myself and find that I lose feeling in this hand very quickly. It goes dead. If I look at it, or if I make a strong movement, then the feeling in the hand comes back. Sometimes, I think I have only one hand." The other sensory defect which Bender described after parietal lesions was an altered duration of the " after-sensation " when a stimulus is removed. Though usually decreased or abolished, on occasions and when cutaneous hypersensitivity exists, it seemed to be prolonged. Here again it is difficult to ignore the all-important role of awareness, and a perusal of Bender's case-reports reveals data which can best be interpreted as phenomena of an attention defect—including even the manifestation of " fluctuation of minimal sensations " (Urbantschitsch, 1875).

Though they have expressed themselves differently, Goldstein, and also Ross and Fountain, have really inculpated a similar psychological mechanism in an attempt to account for tactile extinction. The latter spoke of a " subtle and slight alteration in the consciousness " of their patient with tactile extinction. Goldstein's explanation rests upon the

doctrine of a " utilization of energy " within the nervous system. He assumes that the amount of available " nerve energy " is constant. When a part of the brain is out of action, there is a reduced amount of nerve energy available, and there results a " canalization " of all available energy into one direction. In other words, the brain injured patient cannot adequately deal or cope with two simultaneous tasks—whether these tasks be effector (in the domain of motility) or receptive (sensorial). In such circumstances the weaker percept (or the more difficult task) suffers at the expense of the alternative. Goldstein (1947) also took exception to Bender's use of the word " extinction." As he put it, observation of the phenomenon shows that a stimulus is effective if applied alone, but ceases to become effective under certain conditions, i.e. when two stimuli are applied. This in turn depends upon the " significance of the stimulus to the total organism." Two simultaneous stimuli may be perceived as two, unless they represent " two performances not related to each other which the organism cannot fulfil at once." In such circumstances that stimulus alone becomes effective which " brings about a performance more important for the total organism." Wortis, Bender and Teuber later came round to a somewhat similar viewpoint, and they spoke of tactile extinction as an example of narrowing of the patient's " field," making him " stimulus bound "—to use Goldstein's terminology.

Duncker, in his study of the mutual influence of multiple painful stimuli in normal subjects, found—as already mentioned—that the appreciation of a second (active) pain stimulus caused a drop in the appreciation of a (passive) pain stimulus which had previously been applied and maintained. This author, too, rejected the idea that distraction of attention was responsible for this phenomenon. He found that the drop in sensation occurred in a region which was still " being attended to " . . . " Something was ' drawn away ' but that was certainly not mere attention in the common sense of the word." Duncker considered that the mutual diminishing effect of two painful impulses is due to an " alteration of the central sensibility brought about by the creation of another focus of urgency." By " urgency " Duncker referred to the inherent property of an experience to absorb, to draw towards itself, to become the centre of the total field. A loud noise, a second painful stimulus, a voluntary and forcible muscular contraction, are all, according to Duncker, methods which displace—or which enhance the displacement of—this centre of urgency.

It may not unreasonably be argued that this is a mere terminological quibble, and that Duncker's centre of urgency is merely a manifestation of a more commonplace faculty of attention.

A somewhat similar explanation can be adduced by recourse to the doctrine of " vigilance " of the nervous system as propounded by H. Head (1923). Although he nowhere attempted a definition of this property of " vigilance," by a series of illustrations and analogies, he referred to

a capacity of the central nervous system to react with varying degrees of physiological efficiency depending upon the state of "vigilance" which existed at a given moment. This is not the place to discuss what actually is the nature of Head's "vigilance," but it is clear that for some of his examples the word "attention" can be substituted. Particularly is this the case when awareness of incoming stimuli is being considered. In Head's own words we can read his explanation of what we would today regard as tactile inattention: ". . . The central nervous system exercises selection amongst the diverse and massive physical influences acting on the organism from without; some of these are effective in arousing a neural reply, others pass unnoticed. Each adequate stimulus is followed by an appropriate response which becomes increasingly specific with each rise in functional level. *But if any two are applied together, the reaction which follows does not of necessity express their algebraic summation · more often one is favoured at the expense of the other. . . .*" (My italics.)

Even earlier, Head and Holmes (1911) had emphasized that in parietal cortical lesions, a localized defect of attention lay at the basis of many of the characteristic sensory defects. In their own words. ". . . A portion only of the patient has, as it were, become untrustworthy. We believe that functional integrity of the cortex enables attention to be concentrated upon those changes which are produced by the arrival of afferent impulses. When this is disturbed, some impulses evoke a sensation, but others, from lack of attention, do not affect consciousness. Attention no longer moves freely over the sensory field to be focused successively on fresh groups of sensory impressions. Sensations, once evoked, are not cut short by the moving away of the focus of attention as when cortical activity is perfect. Hence arise persistent sensations and hallucinations which are so prominent a feature after lesions of the cortex. To sum up, we believe that the cerebral cortex is the organ by which we are able to focus attention upon the changes evoked by sensory impulses. A pure cortical lesion, which is not advancing or causing periodic discharges, will change the sensibility of the affected parts in such a way that the patient's answers appear to be untrustworthy. Such diminished power of attention makes the estimation of a threshold in many cases impossible." And later ". . . Now we have shown that the sensory cortex is the organ by which attention can be concentrated on any part of the body that is stimulated. The focus of attention is arrested by the changes produced by cortical activity at any one spot. These are sorted out and brought into relation with other sensory processes, past or present. Then the focus of attention sweeps on, attracted by some other object."

Although Head and Holmes claimed that the sensory cortex was the organ of local attention, it would be going too far to regard all the complex manifestations of general awareness as the perquisite of that region of the brain or even of the parietal lobes. We must distinguish between local attention and general attention. The latter faculty is almost certainly a non-localizable function, to be regarded along the lines of the

Ganzheits-theorie of cerebral activity. If so, it can be and is disturbed by diffuse cerebral lesions, as well as by focal lesions lying outside of the parietal areas, e.g. the frontal lobes.

In the genesis of tactile inattention, however, disease of the parietal lobes plays a significant and highly specific role. This may be explained along three lines. (1) The role of the parietal cortex as an organ of local attention (Head and Holmes) ; (2) the factor of impairment of sensibility leading to the rivalry of contending double percepts of unequal strength ; and (3) the importance of the parietal lobe as the storehouse of past impressions and hence in the building up of a body scheme or *image de soi*. A severe parietal lesion will therefore be followed by defective attentiveness, sensory impairment, and a tendency more or less to neglect the affected side of the body—three considerations which are important in setting the stage for the appearance of tactile inattention.

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ON SPATIAL SUMMATION OF SENSORY STIMULI IN MAN

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INVESTIGATION of sensory function is beset with special difficulties due to the factor of subjectivity on the part of the individual tested. For the greater part we are dependent on what the subject says he does or does not feel. Another source of uncertainty may be found in the method of investigation which also brings in an element of subjectivity on the part of the observer.

One of the methods frequently employed for testing minor differences in sensitivity of the skin is dragging the point of a needle across the surface of the skin. In clinical investigation this method is a useful and perhaps the only reasonable test, by which certain forms of hyperæsthesia can be demonstrated. An analysis of the method has proved useful in regard to many problems dealing with the organization of sensory function. In this way we are activating a process of spatial summation, one of the fundamental properties of the nervous system.

My interest in this field was roused because, in patients suffering from the sequels of starvation. I found zones of hyperæsthesia, especially marked on the breast and upper arm, which at that time (1946) I could not satisfactorily explain. It was reinforced by the reading of Keegan's investigations in patients with radicular syndromes. On these findings he proposed a system of "dermatomes," widely at variance with the classical dermatomes of Sherrington and Bolk, and corroborated by clinical investigations (Brouwer, 1915). The discrepancies are awaiting elucidation.

The various problems finally centred round two main points: first, what is the meaning of hyperæsthesia as such; second, what is the meaning of the characteristic, dermatomelike shape of hyper- and hypo-æsthetic fields.

THE SYNDROME OF HYPERÆSTHESIA

In order to obtain data bearing on the different modes of sensation evoked by drawing a needle over the skin many observations were made on healthy persons. As will be seen later, the conclusions drawn from these observations have been corroborated by findings in patients with affections of the spinal cord and peripheral nerves.

If, in a healthy person, a needle is dragged over the skin surface the

sensation changes as we progress. After a short time the line feels sharper, more painful or, as some people put it, " of higher pitch." The variables involved in this process may be reduced to the following factors :

(1) *Pressure.*—A very light stroke will give less increase in sensation than one at somewhat heavier pressure. This is especially so in the beginning of a series of experiments, and in untrained individuals.

(2) *Speed.*—A quick stroke is less painful than a slow one, even if the pressure of the former is heavier than of the latter.

(3) *Direction.*—A stroke in the longitudinal axis of the arm or leg is less effective than one at right angles to the long axis. On the other hand, stroking in the longitudinal axis of the trunk is more effective than parallel to the ribs.

Making use of these favouring factors a more detailed description of the shift in sensation was made possible. A good many observations have taught us that the changes make up a syndrome in which the following elements may be recognized :

(*a*) In the mixture of various sensations pain grows in intensity. This may occur in the form of a burning pain. Slow stroking may add elements of cold to it. Personally I was never sure of sensations of warmth, the less so since " burning " pain is easily, but not always rightly, associated with a representation of heat.

(*b*) An effective stroke, even if only lightly applied, is followed by a noticeable after-effect. If the same traject is used repeatedly the skin must be rubbed in order to reduce these effects.

(*c*) There are two kinds of changes in localization of the stroke. At the end of a slow stroke an indication of " spattering " is felt, as if fine sparks are coming off. The phenomenon may be described as a spurious movement, and conceived as an effect of irradiation.

Another effect is the misinterpretation in direction as well as in form of the stroke. In stroking at right angles to the longitudinal axis of the arm the stroke is felt as if running in a proximal direction (*see* fig. 1 A). In some subjects one has to stroke quite obliquely, from more proximal to more distal, to give the impression of a transverse line. In many persons a straight stroke arouses the impression of a curve with the convexity in proximal direction, or of two curves, both proximally convex.

The onset of change in quality of sensation is gradual in a stroke parallel to the long axis of the arm. The changes are not only more sudden but also more striking if the stroke is directed at right angles to the longitudinal axis of the limb. After a slight increase at the beginning of the stroke a sudden change occurs over a distance of a few millimetres. The rest of the stroke, although often not so sharp as the short period of transition, remains sharper than the first part. The diagram illustrates the sequence of events (*see* fig. 1 B). The question arises whether this phenomenon is due to the local arrangement of end-organs in the skin or to other mechanisms. There is one strong argument for doubting a

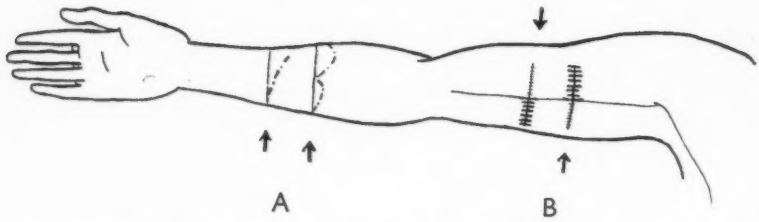

FIG. 1.—A. Defective localization of a stroke with the point of a needle. ——— Objective direction of the stroke. · — · — · — Subjective impression of the same stroke. B. Shift of sensation to the side of pain during a stroke downward and upward at the inner side of the upper arm.

solution based solely on peripheral processes, namely, if the direction of the strokes is reversed, the same sequence takes place and the first part of the stroke is less painful than the latter. The limit between two halves may, or may not, be indicated by a very sharp zone of transition. Now, if we are stroking downwards on the inner side of the horizontally stretched arm the impression grows that the lower part of the skin is more sensitive than the upper. But stroking upward the reverse conclusion presents itself: this time the upper area is more painful than the lower. If this method of testing be used, it appears a general rule that, the *second field seems more sensitive than the first.* As soon as solitary pricks or touches are applied the difference between the two areas disappears, to emerge again after stroking.

If we stroke very slowly it may happen that the painful element of sensation has increased to such a degree that the contrast between first and second field is no longer felt.

It is not necessary to give an uninterrupted train of impulses to obtain this effect. A succession of pin-pricks leads to the same results. If a small strip of adhesive tape is put on the small zone of transition between the two areas the phenomenon is unchanged. This experiment proves, moreover, that excitation of the small zone of transition is not a *conditio sine qua non* for a contrast between the first and the second area. The conclusion is drawn that the difference in sensation following stimulation of the two areas is due to the special mode of testing and is not directly related to the arrangement of end-organs. During the stroke a number of points closely related in space are stimulated one after the other. This mode of stimulation may give rise to the mechanism of *spatial summation.* Without anticipating the question as to how far such a process may include the peripheral nervous system, or must be caused solely by central mechanisms, spatial summation enables us to explain the characteristic shift of sensory quality. It is well known that various elements of sensation differ widely in respect to summation. Whereas tactile impulses do not sum to any appreciable degree, sensations of cold and temperature

do so very markedly. A shift towards the latter modes of sensation might be expected, and this proves indeed to be the case.

It is possible to explain the misinterpretation of localization along the same lines. If a square is drawn on the arm while the object closes the eyes, the form is reasonably well recognized if the head of the pin is used. If, on the contrary, we use the point of the pin, a marked distortion takes place (*see* fig. 2). Apparently the addition of pain impulses is responsible for the distortion.

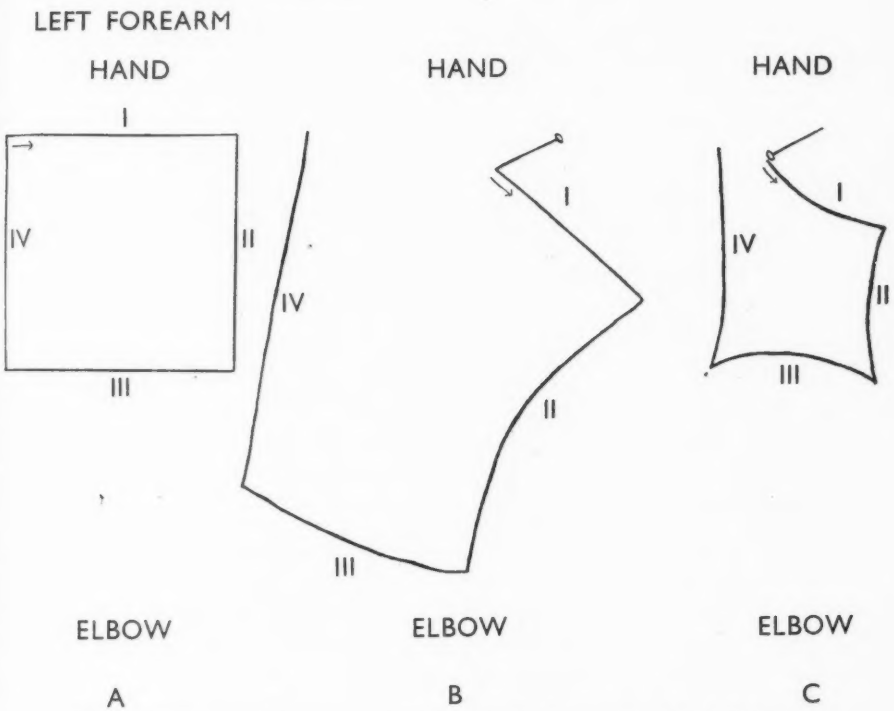

FIG. 2.—With a pencil a square was drawn on the inner side of the left forearm. A. Objective size of the square (5·5 × 5·5 cm.). B. Subjective impression of the square if drawn with the *point* of a pin. Note the proximal displacement of the first side (I), the curving of the lines, the marked enlargement and the slight turning of the whole figure in relation to the axis of the arm. The figure is open instead of closed. C. The same square on the same place of the arm, drawn with the *head* of the pin. Note the progressive decrease in proximal displacement of the first side (I), the smaller size, and the placement of the figure in relation to the axis of the arm.

Summarizing the facts stated above, we conclude that dragging a pin along the skin surface brings about a shift of sensory qualities to the side of pain. Reversing the direction of the stroke does not change the effect.

The findings could not be translated satisfactorily into terms of purely peripheral arrangement of end-organs. They could be explained, however, if a differential influence of a process of spatial summation was taken into account.

The Shape of Hyperæsthetic Areas

If we stroke the inner side of the horizontally stretched arm the increase of pain occurs suddenly, so that on this line a point of transition can be indicated. This point is not a point in a mathematical sense, but a small zone measuring only a few millimetres. If we make a number of strokes parallel to each other, a row of points of transition can be indicated, which, connected with each other, form a line parallel to the longitudinal axis of the upper arm. This line may be prolonged downward to the forearm, but the demarcation there is less pronounced, and careful investigation may bring out more than one line, so that the results may be confusing at first. In the upper arm, however, the findings are clear cut. This line is suggestive of a boundary well known from the arrangement of dermatomes, viz. ventral axial line of Sherrington, " Differenzierungslinie " of Bolk. Along this line areas adjacent on the skin are widely separated in the spinal cord. For example, on the inner side of the upper arm the dermatomes C_5 and Th_2 touch each other on the skin surface.

Similar lines are found over the breast where Th_3 and C_4 come together. The same is found along the borderline of sacral and lumbar segments in the leg. Along all these boundaries a stroke of a pin brings out marked contrasts. Even the boundary between cervical and trigeminal segments above the ear can be shown in many individuals, and in general the second area is more sensitive than the first. Sometimes the differences are clearer if the line be drawn in one direction than *vice versa*. An upward stroke on the thorax may be more effective than a downward stroke. This difference is found in some individuals, though lacking in others.

Since the arrangement of the zones of transition appeared indicative of a mechanism in which dermatomes or dermatome-like areas were represented, my attention was drawn to some spinal mechanism. The observations taught that previous stimulation of C_5 will change the sensory reaction in Th_2 and that, in stroking the other way, the reverse is the case. This would imply a widespread process which is difficult to explain solely as a result of stimulation of the peripheral nervous system, even though the net-structure of the peripheral nervous system and the occurrence of axon branching was fully recognized (Sinclair and others, 1948). The supposition that sensory stimuli are brought to summation by means of spinal processes was expressed by Sherrington more than once in his classical " Integrative Action of the Nervous System." Many data taken from the field of normal anatomy and from observations made in patients with diseases of the spinal cord and peripheral nerves strongly support Sherrington's opinion.

As for the anatomical side, it should be noticed, as was shown many

years ago by Cajal, that incoming fibres of the posterior root spread over more than one segment by means of collaterals. His statements have a special bearing on well-myelinated fibres of large calibre. Only recently has the course of unmyelinated fibres entering the spinal cord been known in some detail. Ranson (1913, 1914) traced unmyelinated fibres through the tract of Lissauer into the *substantia gelatinosa Rolandi*. His hypothesis that thin and poorly myelinated fibres carry painful sensations has been confirmed amply by himself and later investigators, although destruction of the gelatinous substance failed to abolish pain perception in the cat (1915). Therefore the fate of pain impulses after entering the spinal cord remained uncertain. *Kuru* (1938), in a careful study, proved that the cells of origin of the spinothalamic tract are identical with the great pericornual cells round the posterior horn. Not until 1939 was Scentagothai-Schimert able, using the method of "boutons de dégénération," to follow unmyelinated fibres to the same pericornual area, apart from connexions with the *substantia gelatinosa*. Each root spreads to its own segment and to some segments more proximal.

Longitudinal sections through the spinal cord show clearly that the cells of the spinal cord are organized in vertical columns, so that spread of painful stimuli to segments proximal and distal from the segment of entry can readily be accomplished. Scentagothai's findings, namely that fibre connexions exist especially with proximally situated cell groups having a known sensory function, would suggest a spatial arrangement in such a way that incoming impulses from a certain dermatome may encroach especially upon higher situated segments. This point will appear to be of importance for the explanation of the outline of hyperæsthetic areas. From normal anatomy therefore we learn that direct connexions to other segments are available for all modes of sensation.

Observations made in many patients with various affections of the spinal cord and peripheral nerves could be reduced to a simple formula.

The shift to the side of the pain-component was interpreted as a differential effect of summation on the various modes of sensation. We might expect, therefore, that processes inactivating the fibre system conducting pain sensation would counteract the shift towards the painful side, whereas, on the other hand, involvement of the touch component would further the shift and lead to some form of hyperæsthesia. This expectation has been fully realized. In patients with unilateral antero-lateral tractotomy whose sensation of pain was greatly diminished or eliminated on one leg, the characteristic contrast between lumbar and sacral segments was abolished. They felt the pin, but there was no shift and no contrast between lumbar and sacral segments, whereas the other leg yielded normal sensations and the usual symptoms. On the other hand, in patients with disseminated sclerosis, and degeneration of the posterior columns due to pernicious anæmia, the contrasts were clearly felt.

In certain forms of polyneuritis the first component of sensation showing signs of involvement is touch. This condition resembles the syndrome caused by compression of the nerve, which also appears to be related to anæmia of the nerve stem (Lewis and Pochin, 1937). Touch goes first, pain after that. My patients showed not only marked contrasts and minor degrees of hyperæsthesia but also more lines of contrast, nearly parallel to the main axial lines. The same is true of patients with protruding intervertebral discs, where compression and stretching of roots takes place.

Fig. 3A, B, C shows a number of lines of transition in a patient with protrusion of the intervertebral disc between L_5 and S_1. It may be noticed that in most patients with involvement of lower lumbar and upper sacral roots more than one area is found. The form of the areas coincides with the classical dermatomes only at the periphery of the limb, but, in contrast to the latter, the areas extend proximally and may reach the vertebral column. Instead of the wedge-shaped apical dermatomes of Sherrington and Bolk these areas have the shape of long bands. The contrasts between the areas, in case of L_5 and S_1 involvement, is clearer on the leg. A clear demarcation at the upper end of the lower part of the area (i.e. the part congruent with classical dermatome shape) could be shown just below the knee (*see* fig. 3A).

In fig. 3D, taken from another case, the patient had undergone section of the 4th lumbar root. The patient was examined by various methods. On the leg an oval zone was found where very light touches with cotton-wool were often missed. The boundaries with the normal skin were extremely vague. In the centre the decrease of sensitivity to touch was marked. Stroking cotton-wool over the skin was avoided as much as possible. Single pin-pricks were felt less acutely in an area on the dorsum of the foot near the great toe. Dragging the pin along the surface at right angles to the zones of transition brought out the characteristic lines. Even within the area of hypæsthesia zones of transition could be indicated. Similar areas are present in patients with cervical disc protrusion.

The complete scheme of Keegan, as published in his articles and reprinted in Howell's textbooks of Physiology, shows a system of parallel bands covering the trunk and limbs. If these bands represent dermatomes this would imply quite a revolution in neurology. The assumption of band-like dermatomes is not a modern notion, however ; on the contrary, a very old one, older than the wedge-shaped dermatomes of this century. For example, the diagram of Starr (1894) of cervical and upper thoracic dermatomes closely resembles the areas of Keegan. The same arrangement is found in Edinger's diagram (1904), which has still its place in the textbooks of Bing and Villiger. We must remember, however, that the data underlying the schemes of Starr were obtained in patients with transverse lesions of the spinal cord. Consequently a spinal mechanism may be involved in these results. This supposition was substantiated on looking

over the figures of Foerster and Gagel (1932), where the boundaries of painless areas following transection of the spinothalamic tract are illustrated. In a number of patients Foerster made a tractotomy bilaterally, leaving a difference of one segment between right and left side. Transection of the spinothalamic tract at Th_1 on one side, Th_2 on the other, results in crossed analgesia reaching up to Th_2 on one side to Th_3 on the other. The figures show that analgesia reaches further distally on the arm on the side of higher transection. Moreover, all the figures of Foerster and Gagel taken from four different cases show that the zone of analgesia on the upper arm is *broader* contralateral to the side of more proximal transection. The boundary of analgesia, therefore, shifts in a direction parallel to the long axis of the upper arm if one more segment of the spinothalamic tract is involved. The analogy between Foerster's and Starr's scheme is indeed striking.

Comparison between classical dermatomes and areas of hyperæsthesia and of minor forms of hypæsthesia brings out the following differences: (1) The complete outline of areas of hyperæsthesia can be shown only by using a train of stimuli; application of solitary stimuli yields different results. (2) The shape of the areas is different from that of dermatomes. They coincide only at the periphery, but hyperæsthetic areas encroach upon more proximal dermatomes reaching upward to the vertebral column.

Following on the section of one root, disturbance in sensation tested with solitary stimuli is found as might be expected from the schemes of Sherrington and Bolk. There is only incomplete loss of function, due to wide overlap of adjacent dermatomes. If, however, summation is allowed to take place (and then only !) slight alterations in sensory function might be found extending over more proximal dermatomes and showing an arrangement closely resembling Keegan's and Starr's schemes.

(3) Whereas dermatomes show a considerable overlap, Keegan's areas scarcely overlap at all. In this respect they come nearer to Head's areas of hyperæsthesia. In a recent article Keegan (1948) stressed the conformity of his areas with hyperæsthetic areas accompanying herpes zoster. The same is true of some of the hyperæsthetic zones, following paravertebral injection of hypertonic salt solution (Kellgren, 1939).

At the present moment it is difficult to estimate which cells participate in the process of summation, but the evidence so far seems favourable to the assumption, that the cells of origin of the spinothalamic tract are the main source of summation of this type.

Discussion

A discussion covering all the problems of sensory organization is beyond the scope of this paper. A few possible objections have to be met, however.

Interpretation of the facts in terms of the psychological category seems inadequate. Although it is fully recognized that sensation is a psychological

phenomenon, yet the spatial arrangement of the areas cannot be translated into psychological terms. We are dealing with physiological units. More difficult is the differentiation between excitation of the spinal cord and the peripheral nervous system.

Under the influence of the findings of Woollard, Weddell and their co-workers, our view on sensory organization has considerably deepened (Sinclair, Weddell and Feindel, 1948; Weddell, Sinclair and Feindel, 1948). As expressed by Walshe (1942) and Tower (1943), the analysis of sensory function leads to sensory units as elements of sensation rather than to a point-to-point relationship. If one point of the skin is stimulated a network of fibres is activated. Differentiation between two points no longer rests on difference of local signal of the end-organ but on differences in constellation of excitatory and inhibitory states in many nerve fibres, according to Weddell, Sinclair and Feindel (1948). Rarefaction of end-organs leads to decrease of function, impulses being felt less intensely, whereas breaks in the network lead to defective localization, irradiation and an unpleasant feeling. Irradiation, according to this view, mainly rests upon defective activity of the peripheral network and on axon branching. The question arises whether the phenomena described in this paper might not be due to peripheral mechanisms only. In answer to this objection the following may be remarked. If, after some trials, the skin is reddening, due presumably to the activity of peripheral reflexes, the contrasts are felt more acutely but the quality of the sensations and the sequence of events remain unchanged. The processes, underlying Lewis' "painful state," offer too narrow a basis for an adequate explanation of the facts stated above.

If the contrasts were based upon the excitatory state of a peripheral network and on axon branching only, we would expect the relations of space to be different from the process described above. Excitatory states in the peripheral network are more apt to occur in the immediate vicinity of the locus of primary excitation. The reverse is true of our syndrome. As long as the stimulation is restricted to the area of supply of one and the same nerve contrasts are barely perceptible. On the other hand, maximal contrast is felt along lines where dermatomes, represented widely apart in the spinal cord, are adjacent in the skin.

Lines of the type described above have been found by Langelaan (1901) in normal individuals, in tabes by Coenen (1900) and Muskens (1903). The symptoms of hyperæsthesia, especially on the boundary of dermatomes, were ascribed to overlapping. Now in man the maximal extension of dermatomes is not exactly known. Even the method of isolation, as used by Foerster (1932), only brings out the centre of a dermatome, the extension of the border zones (presumably yielding sensations only, if the skin is supplied by more than one posterior root, Winkler and van Rijnberk, 1901) remains uncertain. However, consulting the evidence presented by Foerster's papers, overlap seems

minimal along the axial lines, whereas in our case along these lines the phenomenon is most pronounced.

Relations of space, therefore, plead for some other mechanism. Which part of the nervous system can be held responsible? Undoubtedly integrative and summative processes take place in the cortex and the thalamus. But the study of the literature brings strong support for the assumption that the *type of summation under discussion* is founded upon a spinal mechanism.

To quote Sherrington's "The Integrative Action of the Nervous System" (Ed. 1947), page 185, where the scratch-reflex in the spinal dog is discussed: "A subliminal stimulus applied at a point A will render a subliminal stimulus applied at point B near A supraliminal if the second stimulus follow within a short time, e.g. 500σ. The space of receptive surface across which this can be demonstrated in the scratch-reflex amounts to 5-6 cm." "(But) the phenomenon is characteristically and simply illustrated by the difference between the potency as a stimulus of the edge of a card, say 6 in. long, pressed simultaneously over its whole length against the receptive skin field, say for 5 sec., and on the other hand lightly drawing one corner of the card along the same line in the skin field also for 5 sec. The former application simply evokes a reflex of a few beats, which then dies out. The latter evokes a vigorous reflex that continues and outlasts the application of the stimulus. A successive line is more effective as a stimulus than a simultaneous line of equal length and duration." "If a parasite in its travel produces excitation which is but close below the threshold, its progress is likely to so develop the excitability of the surface whither it passes that the scalptor reflex will be evoked. In the skin and the parasite respectively we have, no doubt, two competing adaptations at work. It is perhaps to avoid the consequences of the spatial spread of the 'Bahnung' that the hop of the flea has been developed."

Discussing the phenomenon of fatigue, Sherrington remarks that a state of exhaustion in one point spreads over neighbouring points: "the resemblance between the distribution of the incidence of this fatigue and that of the spatial summation previously described, argues that the seat of the fatigue is intraspinal and central more than peripheral and cutaneous; and that it affects the different part of the arc inside the spinal cord, probably at the first synapse."

The analogy between motor symptoms in the spinal dog and sensations in man is striking enough. Even the post-stimulatory effect is present. It would seem not too hazardous to assume that the spinal cord, summating impulses which are debouching into a motor effect, might in the same way elaborate sensory impulses.

Quantitative analysis of sensory function in patients with polyneuritis was carried out by Wolff and co-workers (1948), who found that the threshold of pricking pain (i.e. pain of short duration) was raised, whereas the threshold of burning pain (i.e. longer lasting) was lowered.

Stein and von Weizsäcker (1927) also made an analysis of sensation in patients with polyneuritis and affections of the posterior columns. Their investigations were not directed to solitary stimulation but to a series of stimuli. The results are here discussed in some detail because of their remarkable conformity with our findings.

If, in this group of patients, the skin was stimulated with a test hair of Von Frey in a frequency of 3 per second, the first few touches were perceived correctly, but soon some touches were missed. After a short time abnormal sensations appeared, whereby elements of pain and temperature emerged. The correct localization of the stimulus suffered and irradiation was noticed. There was also a marked after-effect. Similar changes were found in neighbouring points. The syndrome was different from disturbance caused by peripheral nerve lesions, in that the latter showed increase of threshold values right from the start, whereas in the former case the threshold rose in the course of stimulation and fell back to previous values after a short period of rest. There was a " lability " of function. The change in quality of the sensations and threshold values, brought to light by successive stimulation, were described as " Funktionswandel." The authors rightly suggested that in this process not only the periphery, but also the spinal cord and central mechanisms play a rôle. In nervous and fatigued persons " Funktionswandel " took place in the same way although to a lesser degree. Similar observations were made by Hut (1936), who, using chronaximetric methods, found in normal people defective differentiation between touch and pain due to fatigue. A gradual transition between hyperæsthesia in normal people and in patients seems warranted.

Concerning the change in localization a few words may be added. In our material a general tendency to dislocate the stimulus in proximal direction became manifest. The same was found by Hall and Donaldson in 1885. Stengel (1927) observed that patients with involvement of the posterior columns transformed transverse tracks into a direction parallel to the longitudinal axis of the limb.

We found that recognition of forms became less accurate under the influence of painful stimuli. This is in agreement with the observation of other investigators that localization of pain in the normal skin is very poor (*see* von Skramlik, 1937, p. 445 *seq.*). The interaction of elements of localization and pain demonstrates once more that integration of sensation on higher levels of the nervous system is dependent on correct functioning of both spinothalamic tract and posterior columns.

It is a general rule laid down in Head's papers on sensation, that in case of sensory disintegration the sensation acquires the characteristics of pain perception, viz. poor localization and marked after-effect. It is not easy to see why this should be so. Some light on these problems is thrown by electrophysiological work of recent years.

In the language of electrophysiology, a shift to the side of pain-compo-

nents implies a shift to a system of " slower " function ; the chronaxy of pain-fibres is higher than the chronaxy of touch fibres, the rate of conduction is lower and the pain potentials have a lower gradient. It is possible, as Adrian (1932) remarked, that a system of slow action works out differently in the spinal cord. Summation, irradiation and slow activity might be three aspects of one and the same state of affairs. If we assume that low gradient potentials enhance the lower frequency activity in the spinal cord (Adrian, 1932, p. 59), the characteristics of pain sensation would be comprehensible. Slow potentials, led from the spinal cord and the brain, are regarded to be the consequence of synchronous activity of a cluster of cells. It is easy to see that within this group of cells no differentiation of activity takes place. Synchronization of many cells has a spatial corollary : summation and defective localization belong together.

In the second place electrophysiology teaches that the " resting " nervous system is not actually resting. Background activity remains, and is sustained for the greater part by the continuous stream of incoming impulses. This principle, worked out for the cortex by Bremer (1938), holds good for the spinal cord. ten Cate, Walter and Koopman (1947) observed a general slowing down of electrical activity of the spinal cord following section of posterior roots in frogs. Horsten found the same in cats (1948). Impulses from the skin proved to be of considerable influence (ten Cate, Horsten and Koopman, 1947). The effect of a stimulus results from the stimulus plus the background activity of the elaborating system. Involvement of posterior roots slows down the background activity of the spinal cord, and in this promotes presumably the painful component of sensation.

Summary and Conclusions

In normal persons the stroke of a pin dragged across the surface of the skin does not produce identical sensations from the beginning to the end. Increase of pain is perceived. The change is more marked if axial lines are passed. After crossing the line, the area " on the other side of the line " yields sensations different from the area " on this side." After reversing the direction of the stroke, the same sequence of events takes place. Diffuse impairment of peripheral nerves (especially if thick fibres are involved) and impairment of function of the posterior columns is apt to bring out the phenomena more clearly. Following transection of the spinothalamic tract the contrasts are abolished. The above observations have been explained on the basis of spatial summation taking place in the spinal cord. The spatial organization of summation would seem to be closely connected with the organization of the spinothalamic tract and its fibre connexions with the posterior roots.

On this basis an attempt has been made to reconcile discrepancies between Keegan's areas and Sherrington's dermatomes.

From these observations it is deduced that certain forms of hyperæsthesia, although eventually conditioned by processes set up in the peripheral nerves, are founded upon spinal mechanisms.

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PLATE XIX

FIG. 3.

To illustrate article by Droogleever Fortuyn.

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FIG. 3A, B, C.—Protrusion of the lumbosacral intervertebral disc. Stroking at right angles to the lines indicated, the patient feels increase of pain. Several areas could be outlined in this patient.

FIG. 3D.—Section of L_4. The sense of touch was diminished on the foreleg. Pinprick was felt less acutely on the dorsum of the foot near the great toe.

Stroking with the needle yielded contrasts as indicated by dots (foreleg) and crosses (thigh).

ON THALAMIC DYSÆSTHESIÆ AND THEIR SUPPRESSION BY BILATERAL STIMULATION

BY

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Introduction

The phenomenon of suppression of sensory stimuli is a commonplace, daily experience in the normal person. The sensorium is continually bombarded by sensory impulses from distance, cutaneous and deep receptors. Many of these impulses never reach consciousness. There is a continual competition for consciousness between impulses representing all the modalities, and reaching the brain from all parts of the body. Visual, auditory, painful or pleasurable stimuli may occupy consciousness to the exclusion, or almost complete exclusion, of all other stimuli. Any sensory stimulus from any part of the body may achieve sensory dominance at any time, provided that the stimulus is strong enough. Attention plays a considerable part in the operation of the sensory mechanisms under normal circumstances.

Oppenheim (1900) seems to have been the first to observe the fact that bilateral sensory stimulation "in certain brain diseases which cause unilateral disturbance of sensibility" may result in failure to appreciate the stimulus applied to the affected side. He suggested that this manner of examination should be called "the method of double stimulation." Head and Holmes (1911) noted that if weights were placed in the hands of a patient with a lesion of the sensory cortex he would, after a while, fail to appreciate the presence of the weight in the affected hand. The reintroduction by Bender and his collaborators of the method of double stimulation has produced interesting results in patients with lesions at various levels in the nervous system, but particularly in those with lesions of the parietal lobe. Bender and Furlow (1945) discovered a patient with a parieto-occipital lesion in whom suppression of visual and tactile stimuli occurred on the affected side of the body on bilateral stimulation. Further observations have been made in the sphere of vision (Bender and Teuber, 1946; Bender, 1946) and also in that of hearing (Reider, 1946). Bender (1945), Nathan (1946) and Ross and Fountain (1948) have published examples of cutaneous sensory suppression, or extinction, and alteration in the sensory adaptation time in patients with parietal or parieto-occipital lesions. The phenomenon varies in degree from a "slight reduction in the sensory adaptation time,

or a rise in the sensory threshold, to complete extinction of sensibility" (Bender, 1945). The same writer reported that no suppression was to be found on double stimulation in patients with lesions of spinal roots and peripheral nerves, but minor and analogous forms of the phenomenon were demonstrable. He also found suppression to be an infrequent happening in patients with lesions of the spinal cord. It is, however, in those with lesions of the parietal lobe that the phenomenon is seen in its fullest form. The effect may be produced by a lesion of either hemisphere. Most patients whose cases have been described were suffering from gunshot wounds, but neoplasm and presenile dementia (Bender *et al.*, 1948) have also been inculpated. Recent experience suggests that the sign is not very uncommon in patients with lesions of the parietal lobe.

In this communication the case of a patient with a large right parieto-occipital glioma is reported. This man presented a thalamic syndrome, affecting the left half of his body, in the later stages of his illness. Stimulation of the left limbs and trunk with pin-prick, heat or cold produced characteristic dysæsthesiæ. Simultaneous bilateral stimulation with identical stimuli resulted in suppression of the unpleasant and painful sensory experiences on the left half of the body, only the stimulus to the normal right side being appreciated.

Case Report

Male, aged 62. *London Hospital Reg. No.* 31228/47.

The patient first attended Doctor Russell Brain's Out-patient Clinic on October 8, 1947. He was admitted to hospital five days later with a presumptive diagnosis of intracranial tumour.

History.—Three months before admission he had an attack of numbness beginning in his left great toe and spreading over the whole left lower limb. The sensation lasted a few seconds. A few days later he had a second attack in which the numbness was accompanied by pins and needles and a cramp-like sensation, but now the dysæsthesiæ spread to involve the whole left half of the body except the face, and there were involuntary jerking movements of the left arm and leg. Over a period of six weeks the attacks grew longer and more frequent, the whole of the left side of the body being involved. There was never any impairment of consciousness, and he insisted that he could have walked in an attack had he wanted. Six weeks after the onset he was admitted to another hospital, where an examination of the cerebrospinal fluid showed no abnormality of pressure or constituents and an X-ray of the skull was negative. The attacks ceased whilst he was in hospital and he had no more during the course of his illness.

Two weeks before admission he noted clumsiness of his left hand. He began to drop things from this hand and could not roll his cigarettes properly. At meals he would carry food to his ear with his left hand instead of to his mouth. At the same time he found dressing difficult, putting on his trousers back to front and his shoes on the wrong feet. No matter how hard he tried he could not correct these mistakes.

One week before admission he began to walk into objects on his left side.

He had one severe headache four weeks before examination, but he was otherwise free from pain. There was slight progressive deafness in the left ear. He had increased frequency of micturition and slight difficulty in starting the act. He had lost 1 stone in weight in the past year. The previous and family history were negative.

On examination the patient was a grey-haired, tall, slim man with a slight dorsal kyphosis. Upper jaw edentulous. General examination otherwise negative.

Central nervous system : External examination of the skull negative. Right handed. No aphasia. Marked apraxia for dressing. No other apraxia. Agnosia for observer's right and left but not for his own. Topographical memory normal.

Mental state : Fully orientated, alert and co-operative. No disorder of mood. Memory normal. Psychometric tests showed the patient to be of average intelligence.

Cranial nerves : Some blurring of the temporal margin of the right optic disc, left normal. R.V. 6/6, L.V. 6/12. Left homonymous hemianopia with macular sparing. No abnormality of the pupils or external ocular movements. Slight deafness in left ear. Other cranial nerves normal.

Motor system (limbs and trunk): Slight pyramidal deficit in the left upper and lower limbs. No wasting or dystonia. Occasional, slow, involuntary flexion and extension of the left elbow. Marked ataxia of left upper limb.

Reflexes : Arm-jerks brisk and equal. Superficial abdominal responses present on the right but absent on the left. Knee and ankle jerks brisk, left more so than the right. Right plantar response downgoing, left equivocal.

Sensation (limbs and trunk) : Impaired appreciation of cotton-wool over the left limbs and left half of the trunk ; impairment most marked over left upper limb and left lower limb below the knee. Appreciation of pin-prick impaired over the left limbs and left half of trunk, but the sharp end of the pin could always be distinguished from the blunt. Slightly defective thermal sensibility over the left limbs. Position sense severely defective in left fingers and slightly so in left wrist. Marked astereognosis and defective two point discrimination in left hand. Vibration sense diminished in left limbs. The effect of bilateral stimulation was not tested at this time.

Cardiovascular system : Pulse 70, normal rhythm. Gross arteriosclerosis of peripheral vessels. Heart normal. Blood-pressure 140/80. *Chest and abdomen* normal, apart from the scars of a bilateral herniotomy. *Examination of the urine* negative.

Investigations.—Lumbar puncture showed no abnormality of cerebrospinal fluid pressure or constituents. W.R. negative in blood and cerebrospinal fluid. X-rays of skull and chest normal. In view of the appearance of the right optic disc air encephalography was not carried out. A percutaneous arteriogram (Mr. J. V. Crawford) showed a normal vascular pattern on the left side. The injection could not be made on the right side.

At this time the patient showed improvement in his apraxia for dressing, and, as there was no other change in his condition, he was discharged from hospital for supervision in the Out-patient Clinic. He remained well for more than three months, being able to dress himself except for his shoes, which always caused him trouble. He was readmitted to hospital on February 26, 1948.

Second admission. London Hospital Reg. No. 30772/1948.

Two weeks before readmission he noticed weakness and clumsiness of his left limbs, which felt cold and numb. If he touched his left leg he experienced a feeling of a red hot needle touching him ; this sensation was also produced by washing his left leg with cold water. He could not appreciate heat with his left hand or leg. His left hand felt cold. He had slight dragging pains in his left leg. His speech became slurred.

One week before admission he noticed that his left leg was uncomfortable after a brisk walk of half a mile. He went to bed, waking in the morning with a severe pain beginning in the anterior aspect of the left thigh and radiating down the left leg. The pain came in paroxysms lasting a few seconds. It was very severe, sharp, " like someone trying to break my leg," and made him cry. He could not bear the weight of the bedclothes, which brought on the pain. Movement precipitated the pains. His left leg was burned with a hot-water bottle. He could not

move his left arm or leg, often losing his left arm which would fall behind his back. He had no headache.

On examination, he had lost more weight and looked very dilapidated. Tongue dry and furred.

Central nervous system : No dysphasia. Apraxia for dressing not tested. No other apraxia. Agnosia as before.

Mental state : Co-operative, alert and fully orientated. Memory normal. Intellectual functions showed no change. Mood labile ; he became very depressed and emotional if his pains were frequent or if sensory testing was prolonged. Very restless, tried to relieve his pain by frequent changes of his position.

Cranial nerves : The optic discs showed no change. Ill-sustained nystagmus to right and left. Incomplete cutaneous anæsthesia to cotton-wool over the distribution of the left trigeminal nerve. Cutaneous hypalgesia to pin-prick, with raised threshold and hyperpathia, over the same area. Left lower facial weakness. Tongue protruded to the left.

Motor system (limbs and trunk) : Severe flaccid paralysis of the left upper limb, most pronounced distally where paralysis was complete ; feeble movements present at elbow and slightly stronger movements at the shoulder. Spastic paralysis of the left lower limb, feeble movements present at the hip and knee only. Right upper and lower limbs normal.

Reflexes : Arm-jerks slightly brisker left than right. Superficial abdominal responses, right present, left absent. Knee and ankle jerks exaggerated, left more than right, with ankle clonus on the left. Right plantar response down, left up.

Sensation (limbs and trunk) : Complete left hemianæsthesia to cotton-wool. Appreciation of pin-prick was normal over the right half of the body. On the left side there was hypalgesia with raised threshold and hyperpathia, especially in the left lower limb, where a firm prick evoked severe pain and a profound emotional response. The pain was " burning and cutting ; like red-hot needles." Irradiation of the pain was marked and localization was grossly defective. On simultaneous stimulation of mirror points on the right and left sides of the body with pin-prick the sensation was completely suppressed on the left side, the stimulus to the right side being normally appreciated. There was thermo-anæsthesia to large temperature ranges over the left half of the body, with over-reaction to higher and lower ranges. This again was most marked in the left lower limb. Suppression of the left-sided stimulus was present on bilateral stimulation. There was no delay in the appreciation of cutaneous stimuli. Deep sensibility was reduced over the left side of the body, with hyperpathia in the lower limb only. Vibration sense was grossly defective in the left limbs. Postural sensibility was absent at the left fingers and very defective at the wrist and elbow. In the lower limbs this modality was absent at the toes, slightly defective at the ankle and normal at the knee, where movements produced severe pain. Two-point discrimination was grossly defective over the left half of the body.

The other systems showed no change not previously remarked. Blood-pressure 120/70. Urine examination negative.

Detailed sensory testing.—(*a*) *Pin-prick :* (i) *Simultaneous stimulation of mirror points on right and left sides of the body with pin-prick.* This test was repeated on innumerable occasions ; the stimulus on the right side was always normally appreciated whilst that on the left was invariably completely suppressed. As long as the right side was stimulated simultaneously, even with the gentlest prick, the most vigorous prick on the left side produced no response in the patient. The phenomenon was present in all parts of the body.

(ii) Measurement of the sensory adaptation time was obviously impossible, but it was noted that if the stimulus to the right side was removed a continued stimulus to the left side was not appreciated for a variable period. Thus, on the forearms the left-sided stimulus was felt on an average twelve seconds after removal

of the right pin ; the reading varied from six to eighteen seconds. Over the feet and legs the latent period averaged seven seconds, with a variation of five to eight seconds. If the left-sided pin was withdrawn after the right, but before the pain was felt, and then immediately reapplied, there was prompt recognition of pain. Similar changes were noted over the trunk and face. These observations were not completed, but the right stimulus was applied momentarily, for three seconds and for five seconds with similar results as regards the length of the latent period.

(iii) *Bilateral stimulation of asymmetrical points on the right and left sides with pin-prick.* Over the face asymmetrical stimulation was effective in producing suppression ; for example the right pin was applied above the right eyebrow and the left above the upper lip. In the upper limbs, however, the left pin-prick was always appreciated if the points stimulated were asymmetrical by more than 2 or 3 cm. A similar state obtained in the trunk. Over the lower limbs suppression occurred even when points as far apart as the first interdigital space on the right and the region of the knee on the left were stimulated together. Simultaneous stimulation of the right arm and left leg did not produce suppression.

(iv) *Bilateral stimulation with different modalities on the two sides.* The application of Bárány's noise-box to the right ear, or of bright lights to the right visual field, did not suppress pin-prick on the left side. Similarly thermal and tactile stimuli to the right limbs failed to cause extinction of the painful stimulus on the left.

(v) The tests were performed firstly with the eyes closed, and secondly with the eyes open and attention directed to the site of stimulation on the left side. Identical results were obtained in each case.

(*b*) *Thermal sensibility :* Temperatures between 18° C. and 60° C. were not appreciated over the left upper limb. For instance, a stimulus of 22° C. produced the response, " neither hot nor cold, hot sensation, something warm." Temperatures over 60° C. were " very hot, unpleasantly hot." The range of non-appreciation was smaller over the trunk and lower limb, between 25° C. and 50° C. Cold over the trunk was felt as " intense cold, very unpleasant, a sort of hot and cold," whilst heat was felt as " unpleasantly hot." The response to thermal stimulation of the left lower limb was almost catastrophic, that to cold being the more profound. Heat gave him a feeling of " great heat, unpleasant heat, an awful pain" ; cold made him cry " very cold, a sharp pain, a burning pain ; you would not do this to me if you knew how much it hurt, Sir. You don't realize how much it hurts." There was some impairment of thermal sensibility over the left side of the face with a moderate over-reaction, more to cold than heat.

Thermal sensibility was normal over the right side of the face and the right limbs. Thermal stimuli were uncomfortably hot or cold over the right side of the chest and abdomen, though the feeling was quite different from that on the left. He jumped whenever he was touched with a hot or cold tube on the right trunk. It was thought that this reaction possibly indicated a hyperpathia on the right side, but the patient attributed his reaction to a fear that he was about to be stimulated on the affected left side.

(i) *Bilateral stimulation of mirror points with identical temperatures.* This test always resulted in suppression of the painful thermal sensation on the left side. The suppression was complete. This was most dramatic in the case of application of cold to the lower limbs ; bilateral stimulation resulted in appreciation of the right-sided stimulus alone, then a single application of cold to the left leg would cause a paroxysm of agony.

(ii) *Bilateral stimulation of asymmetrical points on the two sides.* Asymmetry of the two points stimulated did not prevent the occurrence of suppression in the left limbs, but over the trunk stimulation of mirror points was required to obtain the phenomenon.

(iii) *Persistence of suppression.* The right-sided stimulus was withdrawn as soon as it was appreciated ; when a hot stimulus was used perception occurred seven

seconds later on the left limbs and trunk, when cold was used the stimulus was not perceived in one minute in the left leg.

Immediate reapplication of cold caused the characteristic response previously described.

(iv) *Bilateral stimulation with differing modalities.* Auditory, visual, tactile or painful stimuli to the right side did not suppress thermal stimuli on the left.

(v) All tests were performed with eyes open and closed.

(*c*) *Deep pressure pain and deep sensibility :* This was normal on the right side. In the left upper limb there was a gross defect with poor localization. There was no hyperpathia. In the lower limb sensibility was reduced, and recognition of the stimulus required two or three seconds ; it was then perceived as a " pressure and an uncomfortable pain." Suppression was present on double stimulation in the lower limbs. In the arms the gross loss of sensation made testing difficult, but suppression was present.

(*d*) *Vibration sense* was tested with a tuning fork (C. 128). Appreciation was just present at the left carpus and tarsus. Application of the fork to the left wrist caused a sharp, local pain and to the left lateral malleolus a sharp pain in the left thigh. Complete suppression was present on bilateral stimulation.

(*e*) *Postural sensibility :* The gross defects rendered testing unsatisfactory. Suppression was probably not present.

(*f*) *Testicular sensibility :* Normal on right. Considerable diminution on the left, but on very firm pressure a sensation similar and equal to that on the right was obtained. Suppression was not present.

Progress.—The left arm rapidly became spastic. Repeated sensory testing showed slight variations in the degree of hyperpathia, and there was a slight delay in the appreciation of pin-prick and thermal stimuli over the hyperpathic areas. The spontaneous pains in his left leg were persistent but varied in frequency. Hot-water bottles were applied to the right side of his body in an attempt to relieve the pain. Coincident with this measure there was freedom from pain for forty-eight hours, the longest respite he had. The pain then returned, and a repetition of the manœuvre met with no success. The pains became almost continuous and began to involve the left upper limb and the back. He became emotionally labile and intolerant of sensory testing. He became drowsy and died in coma on April 3.

Pathological Report. London Hospital. P.M. No. 123/48.

Summary of necropsy.—Bronchopneumonia. Spongioblastoma multiforme of right parietal region invading basal ganglia.

Extensive bronchopneumonic consolidation and purulent bronchiolitis of lower lobes of both lungs. Petechial hæmorrhages and recent fibrinous pleurisy in diaphragmatic pleura on both sides. Severe atheroma of coronary arteries and throughout aorta. Slight central congestion of liver. Soft congested spleen. Small cortical cyst in right kidney. Cortical adenoma ($4 \times 2 \times 1$ cm.) in right suprarenal. Diverticulosis of colon. Moderate myo-adenomatous hyperplasia of prostate.

Examination of the brain after fixation.—The brain, after dissection and inspection of the main cerebral arteries, was suspended and hardened in 10 per cent formaldehyde.

Macroscopic examination.—There was no visible abnormality in the leptomeninges and cerebral arteries, save a few flecks of atheroma in the smaller branches of the right middle cerebral artery, not occluding the lumen. A slightly sunken, pultaceous, yellowish-brown area, measuring 6 up to 3·5 cm. from before back, and resembling an old infarct, lay immediately posterior to the right post-central gyrus, extending obliquely backwards from the ascending terminal limb of the right Sylvian fissure to within 3 cm. of the great longitudinal fissure, involving the supramarginal gyrus. The post-central gyrus appeared superficially intact.

Horizontal sections, made 4 cm. and 5·5 cm. (fig. 1) below the vertex of the brain,

displayed an ill-defined glioma (7 × 5·2 cm.) at the site of the "infarct." The tumour extended forwards to undermine the Rolandic fissure, whilst posteriorly a spur of pultaceous softening extended in the white matter to within 1·8 cm. of the occipital pole. Medially the neoplasm reached the wall of the lateral ventricle immediately posterior to the head of the caudate nucleus. The post-central gyrus was therefore completely undermined by the tumour. The centre of the tumour was yellow and necrotic, but towards the periphery it was firm, grey and injected. The included blood-vessels were greatly thickened. The posterior half of the tumour was yellowish-brown and friable with the characters of an old infarct.

Coronal sections of the remaining basal part of the brain, at intervals of approximately 0·5 cm., showed no abnormality in the basal ganglia anterior to the level of the corpora mammillaria. Here the tumour, encroaching from the upper part of the Island of Reil, reached the border of the putamen, and, at the next level examined, invaded this nucleus and produced softening of the globus pallidus. The next section, in the plane of the crura cerebri and red nuclei, showed replacement of the whole of the right lenticular nucleus by tumour and softening of the internal capsule. The softening extended to the lateral nucleus of the thalamus at the level of the lateral geniculate bodies (fig. 2 (5)) the dorsal part being more affected than the ventral. At the level of the hind end of the geniculate bodies (fig. 2 (6)) the thalamus was greatly softened and reduced in size, the softening being greatest laterally. The softening, in subsequent sections, involved the whole of the pulvinar. The tumour thus approximated towards, but did not appear to infiltrate the thalamus. Posteriorly it extended to within 1·8 cm. of the occipital pole. The brain-stem and cerebellum appeared normal.

Microscopic examination.—Portions of the tumour and all six coronal sections of the right and left thalami were embedded in paraffin wax. Sections were stained with Ehrlich's hæmatoxylin and eosin, Weigert's hæmatoxylin and van Gieson, Weigert's elastic stain and neutral red, phosphotungstic-acid hæmatoxylin, Nissl, and Loyez' hæmatoxylin.

The tumour is an example of spongioblastoma multiforme, the vascular changes so frequently observed in this type being conspicuous. Recanalization of organized thrombus is a feature of a number of arteries at the junction of the growth with the infarct in its posterior border. The right thalamus shows marked pathological changes. In the areas where macroscopic softening was noted there is severe, but uneven, degeneration. At its posterior extremity the lateral border of the thalamus is invaded by tumour ; more anteriorly the changes are due to softening and œdema. Degeneration and gliosis are most pronounced in the pulvinar, all neurones having disappeared except in a narrow peripheral zone along the ventromedial border. The architecture of the lateral nuclear mass is completely disordered in its posterior part, and the individual nuclei are not identifiable. There is considerable diffuse destruction of the myelin sheaths in this region with complete disappearance of neurones and marked gliosis. The neural tissues as a whole are grossly œdematous. Anteriorly, although there is some compression of the thalamus, the configuration of the lateral nuclear mass appears normal, and the posterolateral and posteromedial ventral nuclei are well seen (fig. 3). Intermediately there is a gradual progression to normality. Anteriorly the posterolateral and posteromedial ventral nuclei both contain preserved nerve cells (fig. 4). The material available does not allow of an accurate cell count, but at a rough estimate there are in these nuclei rather more than a third of the number of nerve cells present on the normal side. These cells show chromatolysis, eccentricity of nuclei and other degenerative changes ; in some cells the changes are not in excess of those seen on the normal side, but in many the degeneration is more advanced. In the intermediate sections, between the posterior zone of total destruction and the preserved anterior region, the degeneration is uneven, and here some preserved large nerve cells are visible in the nuclei. The remainder of the lateral nuclear mass shows no cell loss except

where it is invaded and softened by tumour. The dorsomedial nucleus is the least affected of the nuclei. There is œdema and pronounced loss of nerve cells posteriorly, the changes being most marked laterally and decreasing as the ventricle is approached. Anteriorly the nucleus and its neurones are well preserved. The dorsal tubercle is well seen. The centromedian nucleus is involved by œdema and softening posteriorly, anteriorly it is clearly delineated (fig. 3). Examination of the preserved part of the nucleus shows a marked loss of neurones. The posterior commissure is identified on the left side only, and here no changes are detected in the nerve fibres. The left basal ganglia, which served as a control series, appear normal.

Discussion

The clinical findings in this patient conform with those reported by other workers. It was clear that attention played no part in the production of the suppression. Bender (1945) noted that suppression or dulling of sensation was most prominent when corresponding areas of the two sides of the body were stimulated. This was true of the patient reported, although the findings varied with the modality used and the part of the body tested. To obtain suppression over the trunk it was necessary to stimulate mirror points, whether thermal or painful stimuli were employed. In the left upper limb symmetrical stimulation was required to secure suppression of pain on the left side, with thermal stimuli separation of the stimulated points was effective. Wide asymmetry of the points of stimulation in no way affected the occurrence of suppression in the lower limb, no matter which modality was used. Suppression was never achieved when different limbs were stimulated on the two sides of the body. Homolateral double stimulation was not investigated. The application of identical stimuli to both sides was required to obtain suppression. The effect of painful and thermal stimuli to the normal side on the response to less potent stimuli to the affected side was not investigated. Bender (1945) describes one case with a cerebral lesion in which suppression could be produced by the simultaneous application of different stimuli, such as a painful stimulus to one side and a tactile stimulus to the other, and vice versa. It was not feasible to measure the sensory adaptation time on the affected side in our patient, but it is noteworthy that suppression continued after the application of a momentary stimulus to the normal right side ; in the case of cold to the lower limbs this would seem to have persisted for an indefinite period. Withdrawal of a suppressed stimulus was not appreciated. The attempt to relieve the spontaneous pains, which made the patient's life a misery, by the application of warm hot-water bottles to the normal side of the body met with temporary success. A repetition of the manœuvre failed.

The Mechanism of Sensory Suppression

The occurrence of suppression of sensory stimuli as a normal part of sensory experience has already been mentioned. Attention and the general prepotence of painful stimuli are obviously factors of great

importance, but it also appears that one stimulus may directly affect another at the cortical level. Gellhorn (1947), working mainly with cats, showed that "afferent impulses elicited by mechanical or electrical stimulation of the sciatic nerve excite the suppressor as well as the sensorimotor areas of the cortex." Gellhorn and Barker (1947) found that electrical stimulation of the suppressor areas caused "not only a diminution or suppression of cortical activity but also a diminution or suppression of the cortical effects induced by afferent somatic and visceral stimuli." This suppression included afferent visual and auditory stimuli. Cortically induced suppression acted primarily on the ipsilateral cortex. These experimental results suggest that there may be a direct element of mutual inhibition between simultaneous, or approximately simultaneous, sensory stimuli. The strongest stimulus, that is the one which produces the widest pattern of excitation and inhibition, achieves sensory dominance. If such a mechanism as this does operate in the normal human, bilateral cortical representation of sensation might be expected to form the anatomical basis for the process. There is a good deal of evidence to support the existence of bilateral sensory cortical representation in man (*see below*), and Glees (1944), working with macaque monkeys, found evidence that fibres pass from the medial fillet, after it has reached the thalamus, to the opposite thalamus and globus pallidus via the posterior commissure and dorsal supra-optic decussation respectively. These findings have been criticized by Peyton and Rasmussen (1948), largely on technical grounds, but they are obviously worthy of further investigation. Chang and Ruch (1947) have shown that in the spider monkey some spinothalamic fibres decussate in the dorsal part of the posterior commissure, terminating in the nucleus ventralis posterolateralis of the opposite thalamus. They believe that these fibres form the anatomical basis for ipsilateral representation in the thalamus and cortex. The same workers (1949) have demonstrated the presence of fibres of spinal origin in the ventral supra-optic (Gudden's) commissure.

If similar structures and mechanism were shown to be existent and operative in man they would go some way towards explaining the processes involved in sensory dominance. As yet, however, it has proved difficult to demonstrate the presence of suppressor areas in man, and therefore further speculation appears ill-timed.

Sensory Suppression in Lesions of the Sensory Pathways

When the sensory apparatus is disordered by disease or injury bilateral stimulation may reveal the presence of sensory suppression in a pathological form. Under these conditions double stimulation uncovers the competition for consciousness. This sensory manifestation may occur in patients with lesions of the spinal cord, but the full clinical picture is usually seen in those with lesions of the parietal lobe.

The question arises as to which lesion was responsible for the presence of suppression in the patient described. The dramatic escape from

thalamic dysæsthesiæ if both sides of the body were stimulated simultaneously was remarkable. Unfortunately double stimulation was not attempted when the patient was first seen, that is before the thalamic symptoms developed.

The clinical picture presented at this first examination was typical of a right parieto-occipital lesion. The considerable preprioceptive defect and the apraxia for dressing were evidence of disturbed awareness of the left half of the body. There was also defective cutaneous sensibility over the left side. Lesions of the parietal cortex and subcortex have been shown to be the common cause of suppressive sensory phenomenon, and this is to be expected, for it is in this area, the highest sensory level, that a lesion may most easily produce a disorder of consciousness of part or parts of the body. In these circumstances it is likely that suppression would have been demonstrable at this time, that is before the thalamic symptoms appeared. At first sight it would appear improbable that the thalamic lesion was the cause of the suppression, on the contrary, the sensory experiences evoked by stimulation of pathways leading to the affected thalamus might have been expected to exclude the stimuli from normal areas from consciousness. This is probably true of less severe thalamic lesions. Through the courtesy of Doctor A. E. Clark-Kennedy the writer was able to examine a patient with a presumed vascular lesion of the thalamus.

A woman, aged 57, suddenly developed a right hemiplegia from which she ultimately made a complete functional recovery. From the beginning of her illness, however, she complained of sharp, stabbing pains in the right upper limb, chiefly in the fore-arm, and also of feeling of tingling whenever the right half of the body was touched. On examination, two years after the onset of symptoms, she was found to be of rather poor intelligence. There were minimal right-sided pyramidal signs. There was no sensory loss, but stimulation of the right half of the body with pin-prick produced an unpleasant tingling sensation, quite different from the feeling experienced when the left half of the body was stimulated. On bilateral stimulation with pin-prick there was no suppression or dulling of the dyæsthesiæ on the affected right side.

The thalamic lesion in this second patient was obviously in no way comparable quantitatively with that in the first. It is not possible to escape the conclusion that under certain circumstances a thalamic lesion may be responsible for the appearance of suppression, that is if there is sufficient destruction of proprioceptive connexions and of the pulvinar. Under these conditions a sectional disturbance of consciousness of the affected side could occur. In the first patient the lesion did in fact almost completely destroy the pulvinar, whilst on clinical examination proprioception was found to be gravely impaired. It is therefore possible that either or both lesions may have been responsible for the suppression in this patient, though the parietal lesion seems by far the most likely of the two.

The phenomenon of sensory suppression is an inconstant finding, and

its presence presumably depends on the quantity and quality of the injury to the sensory pathways. From the evidence available it appears that a destructive lesion of the highest sensory levels, that is the parietal cortex and subcortex, in some way places the affected side of the body at a disadvantage in the competition for consciousness. A lesion of the thalamus may produce the same effect by reason of interruption of the thalamo-parietal connexions. Spinal lesions rarely cause a similar disorder; this may be regarded as an expression of the level of the lesion in the sensory pathway; if a spinal lesion produces both cutaneous sensory disturbances and a sufficient impairment of consciousness for the affected part, by involvement of proprioceptive fibres, there seems no reason why sensory suppression should not occur. Two patients with spinal lesions producing painful dysæsthesiæ on cutaneous stimulation but little or no postural loss have been examined. In neither case did either homolateral or bilateral double stimulation result in suppression of the abnormal sensory experience.

In the patient reported there was initially a parietal lesion, followed, after several months, by a thalamic lesion. Under these circumstances any sensory stimulus employing the disorganized mechanism had but a tenuous hold on consciousness; indeed such a stimulus though producing an overweening sensory experience when operating alone, was completely suppressed when its course was opposed by competing stimuli from the normal part of the body. How was this suppression accomplished? Returning to the question of mutual inhibition of stimuli from the two sides of the body: if there is bilateral cortical sensory representation in man, achieved by means of similar pathways to those described by Glees and Chang and Ruch in lower animals, it is difficult to see how this could have had a hand in the production of suppression, for both ipsilateral and contralateral fibres would have been equally involved in the thalamus and in the thalamoparietal projections. The tendency would then have been towards bilateral disturbances of sensibility rather than towards suppression of the disordered sensation on the primarily affected side. There is, in fact, a suggestion that this occurred. In the light of present knowledge the nearest approach to an answer to the problem appears to lie in the fact that the patient's consciousness of the left half of his body was disordered. There was gross loss of position sense, and he would often lose his left arm or leg. There was no anosognosia, but his apraxia for dressing (Brain, 1941) was an indication of disorder of his body image. He also had an agnosia for the examiner's right and left sides. The patient was so nearly unconscious of his left side that stimulation of the normal right side at once captured attention, severing the feeble hold of the left side on consciousness. It does not seem possible to say more than that the patient was suffering from a "sectional disturbance of consciousness" (Martin, 1949). It must be admitted that the need for the use of symmetrical and identical bilateral stimulation remains a difficulty. This suggests that although there was defective awareness of the

whole left half of the body the disturbance of consciousness for painful sensory stimuli was not only sectional but also relative. Painful and thermal stimuli could still achieve sensory dominance if opposed by visual, auditory or tactile stimuli to the other side. Perhaps it was too much to expect that there would be a sufficient sectional disturbance of consciousness to enable weaker stimuli to suppress the reverberating response to pain or temperature. Nevertheless, it might have been expected that pain would suppress temperature or vice versa. Evidently, in this case, the appeal to consciousness of a pain-producing stimulus could only be resisted by an identical stimulus, it does not therefore seem possible to relate the mechanisms in the patient to those involved in sensory dominance in the normal human.

The Thalamic Dysæsthesiæ

The second major problem which the patient presented was in relation to his thalamic dysæsthesiæ. Where and how were these felt ? The problem is an old one and has provided a frequent field for combat. A study of the lesions in the brain of our patient, combined with an examination of recent clinical, anatomical and physiological work, may shed a little further light on the subject. The term dysæsthesiæ is used to connote both the hyperpathia and the pain of thalamic disease.

It has been shown that in the brain of this patient a large glioma completely interrupted the fibres running between the sensory receptor nuclei of the thalamus and the parietal cortex on the right side. Secondly there was severe damage to the right thalamus. The most extensive destruction was in the pulvinar, which was almost completely destroyed. The posterolateral and posteromedial ventral (PLV and PMV) nuclei, the sites of termination of the medial fillet and lateral spinothalamic tract, were disorganized posteriorly, but anteriorly, where the nuclei had escaped direct damage from the tumour, there was an incomplete loss of nerve cells, in spite of the severance of the thalamoparietal fibres. This severance must have been present for some time before death. Further surviving nerve cells were seen in the intermediate parts of the nuclei, where degeneration was patchy and uneven. The surviving cells were of the two types mentioned by Sheps (1945), large cells with well-defined, dark-staining tigroid bodies being especially prominent in the posteromedial ventral nucleus (fig. 4). The survival of large cells in these nuclei after severance of cortical connexions has been described by Sheps (1945), who suggested that they were the anatomical site of consciousness and that they formed most of the thalamostriate connexions. The extensive involvement of the striatum in the present patient renders it unlikely that the cells do project to that region ; further the striatal lesions are reflected in the cell loss in the centromedian nucleus (McLardy, 1948). It is possible that the projection may be to pre-Rolandic areas. De Barenne (1924) showed the wide extent of the somatosensory cortex

in the monkey. There is also the experimental evidence afforded by electrical cortical stimulation in man, both Horsley (1909) and Penfield and Boldrey (1937) obtained sensory responses from the motor cortex and other areas beyond the area postcentralis of Brodmann. Several workers have suggested that sensory connexions exist between the thalamus and the precentral motor cortex; the present state of knowledge is well summarized by Walker (1944). From the extent of the lesion in the present patient (fig. 1) it seems unlikely that any thalamo-frontal connexions of this type would have survived. The study of material from patients who have undergone prefrontal leucotomy does not suggest that the projection is to other parts of the frontal lobes. Undoubtedly the most attractive thesis is that these cells connect with the dorsomedial nucleus, though support for this idea must rest mainly on the work of the electrophysiologists. This subject will be returned to later. The outflow from the dorsomedial nucleus to the frontal lobe was well preserved. The remainder of the sensory pathways were intact.

It is apparent that sensations cannot enter consciousness below the upper part of the pons (Walker, 1943). The available sites at which the dysæsthesiæ might have reached consciousness in our patient are as follows: (1) the opposite hemisphere; (2) the tectum of the mid-brain on the affected side; (3) the right thalamus; (4) the frontal lobe on the right side. These will be considered in turn.

(1) *The opposite hemisphere.*—There is a good deal of evidence to support the view that cortical representation of sensation is bilateral. De Barenne (1935), working with cats, demonstrated that strychninization of the sensory cortex of one hemisphere produced hyperæsthesiæ on both sides of the body. Marshall *et al.* (1942) were able to record responses from both sensory cortices when cutaneous stimuli were applied to one side of the head of a monkey. Berry, Karl and Hinzig (1947) have recorded the arrival of sensory impulses in both cortices on stimulating one sciatic or saphenous nerve in the cat. The work of Chang and Ruch on the second decussation of the spinothalamic tracts has already been mentioned. In man various experimental and clinical observations suggest that bilateral representation is more certainly true of the face and head than of the remainder of the body. Penfield and Boldrey (1937) occasionally obtained bilateral sensory responses on stimulating the face or head area on one side. The cases of hemidecortication in man reported by Dandy (1928, 1933), Gardner (1932) and Walker (1943) showed relative or complete recovery of cutaneous sensibility in the trigeminal area after the operation. In Evans' case, which Walker quoted, pin-prick was appreciated equally on both sides of the face five days after operation. Walker believes that this early recovery of sensibility rules out the possibility that the stimulus could have been appreciated in the intact thalamus on the decorticate side, a fact which had been suggested by Fulton and Walker's (1938) work on decorticate chimpanzees. His

conclusion seems eminently reasonable. In some of the reported cases varying degrees of sensibility returned elsewhere on the affected side after some time, sensation over the trunk and limbs reaching approximate normality in Evans' case. Dandy commented on the retention of some degree of position sense, which was also present in our case.

These observations do not suggest that in a man with one intact hemisphere sensory stimuli from the ipsilateral side should be interpreted as dysæsthesiæ on reaching consciousness in the intact hemisphere. Further, there was no interference with the posterior commissure in our patient, and so there is no possibility that a disturbance of the decussating spinothalamic fibres, if such exist in man, was responsible for the dysæsthesiæ being felt in the opposite hemisphere. It is therefore felt that in our patient bilateral representation has no bearing on the presence of dysæsthesiæ. There was a suggestion in our patient that bilateral dysæsthesiæ were present over the trunk. If these were of real significance on the intact right side they were certainly of a different quality and quantity from those on the left.

(2) *The tectum of the mid-brain.*—Walker (1943) has drawn attention to the possible role of the pretectal and tectal regions of the mid-brain in the appreciation of sensory stimuli. He points out that the spinotectal tract ends in the inferior colliculus, and this tract is believed to mediate pain impulses. It is also possible that some fibres from the spinothalamic tract end in this region; but this belief is not clearly founded. The relatively small number of spinothalamic fibres found to terminate in the thalamus (Walker, 1940; Gardner and Cuneo, 1945) is explained, at least in part, by the work of Chang and Ruch. There may also be technical reasons for these disappointing results. From the tectal and pretectal nuclei fibres run to the parafascicular and centromedian nuclei of the thalamus (Rioch, 1929; Le Gros Clark, 1932), but it is unlikely that these pathways have any sensory significance. Arguing from a case of thalamic dysæsthesiæ in which both the lateral (posterolateral ventral) and dorsomedial nuclei had been damaged, Walker suggested that the tectum might be a region where "stimuli of a low order and closely related to feeling tone were appreciated." This theory is difficult to disprove, but the decreasing importance of the spinotectal tract as the phylogenetic scale is ascended renders it unattractive. As higher tractotomies are performed in the brain-stem in man further clinical information on the point may become available.

(3) *The thalamus.*—It cannot be denied that the dysæsthesiæ may have reached consciousness in the thalamus, as Head and Holmes (1911) thought. Nevertheless the occurrence of similar dysæsthesiæ with both supra and infrathalamic lesions and the results of hemidecortication in man lead one to search for other possible explanations of the production and appreciation of these disordered sensations. All writers appear agreed that for the production of thalamic dysæsthesiæ damage to the lateral nucleus of this organ is essential (Déjerine and Roussy, 1906;

Roussy, 1907; Head and Holmes, 1911; Ajuriaguerra, 1937; Riddoch, 1938, and others). Walker (1938) remarks that the site of the lesion in the lateral nucleus involves the terminations of the medial lemniscus and spinothalamic tracts (the posterolateral ventral nucleus). The posteromedial ventral nucleus is often spared, accounting for the escape of the face from the sensory disturbances and pain in these cases. The progression of the pains in our patient, with the spread of pain from leg to arm as the lesion marched medially, illustrates the somatotopic arrangement within the lateral nucleus. On examining the thalamus of the patient there are two remarkable features, firstly the preservation of nerve cells in the lateral (PLV and PMV) nucleus, and secondly the relative escape of the dorsomedial nucleus. This preservation of the dorsomedial nucleus is not uncommon in other reported cases of thalamic dysæsthesiæ in which post-mortem examination has been achieved. There are exceptions, such as the cases quoted and reported by Roussy (1907), Ajuriaguerra (1937) and Walker (1943), where varying degrees of softening were noted in the centromedian and dorsomedial nuclei, but the dorsomedial nucleus is rarely completely destroyed. Hæmorrhage into the thalamus may produce severe thalamic dysæthesiæ with complete destruction of the whole organ and early death (Ajuriaguerra, 1937), but this type of lesion can hardly be brought into the discussion for many and obvious reasons. Head and Holmes (1911) suggested that in the thalamic syndrome the impulses arriving in the lateral nucleus passed medially instead of proceeding to the cortex, and that there they reached consciousness in the essential organ of the thalamus. Ruch (1947), in a very guarded footnote, refers to the possible role of the dorsomedial nucleus in the production of the thalamic syndrome. This likelihood had appealed as an explanation of the occurrence of pain of peculiar character in thalamic lesions, and particularly in the patient described, in whom the available sensory apparatus was such a sadly depleted affair.

The dorsomedial nucleus.—The development, connexions and functions of the dorsomedial nucleus have been described by Le Gros Clark (1932) and Walker (1938). The connexions of the nucleus with the hypothalamus in monkeys are well known (Le Gros Clark, 1932; Le Gros Clark and Boggon, 1933). Le Gros Clark (1932) states that there is no evidence that the nucleus receives fibres from the fillets, nor has any further evidence been produced to suggest that such is the case. The nucleus is intimately related to fibres which pass through the internal medullary lamina, especially from the lateral and centromedian nuclei. Walker (1938) notes that neurones in an intermediate state of degeneration remain in the thalamic nuclei, especially in the lateral nuclear mass, after decortication of primates, and he suggests they are intercalated neurones, which were postulated by Head and Holmes in 1911. Sheps' findings (1945) and those in the patient described show an even greater preservation of nerve cells after clinical ablation of the sensory cortex in man, and it seems likely that these cells do in fact act as intercalated

neurones, connecting the lateral and dorsomedial nuclei. They may thus mediate sensory impulses from the lateral to the dorsomedial nucleus. Le Gros Clark and Boggon (1933) and Mettler (1947) have described the connexions of the nucleus with the frontal lobes in monkeys. More recently Meyer *et al.* (1947) and Freeman and Watts (1947, 1948a) have demonstrated the projections of the various subdivisions of the nucleus to the frontal cortex in man. Their examination of the brains of patients who had been subjected to prefrontal leucotomy showed that the nucleus projects to areas 8, 9, 10, 11, 12, 45, 46 and 47 (Brodmann).

On the physiological side De Barenne (1935) found that in the cat strychninization of the dorsomedial nucleus produced the same sensory symptoms as those which appeared when the same procedure was applied to the sensory cortex or the lateral nucleus of the thalamus. Murphy and Gellhorn (1945), using De Barenne's technique, found that stimulation of the posterior hypothalamus caused bilateral firing in the dorsomedial nucleus, whilst strychninization of the dorsomedial nucleus produced firing first in the ipsilateral and then in the contralateral cortex. Strychninization of the lateral nucleus also caused firing in the dorsomedial nucleus. It is well known that caution is required in the interpretation of experiments in which this technique is employed (De Barenne, 1935), but the results obtained by these workers suggest that the dorsomedial nucleus lies somewhere along the sensory pathways.

Destruction of the dorsomedial nucleus produces "disorientation, incontinence, masking of the face, plateau speech and abolition of the emotional component of the psychosis. Clinical improvement is comparable with that seen after leucotomy" (Spiegel and Wycis, 1948). Smyth and Stern (1938) have remarked on the early onset of mental deterioration in patients with thalamic tumours which originate in the subependymal glial layer and involve the medial areas of the organ first. Riddoch (1936) described two patients with third ventricle tumours who presented with progressive dementia; the second patient showed "emotionalism" which Riddoch ascribed, with reservations, to invasion of the medial parts of both thalami by tumour.

The functions of the nucleus have been variously suggested by different authors. Head and Holmes considered that it, or at least the "medial" nucleus, formed the essential organ of the thalamus, responsible for appreciating the affective quality of a sensation. Le Gros Clark considers, on the evidence of development, anatomy and physiology, that it is related to visceral mechanisms (1948). He believes that the nucleus is a relay station for transmission of impulses originating in the hypothalamus, also remarking that "impulses to the frontal lobes from the nucleus are the resultant not only of the activities of the hypothalamus but also of the activities of the thalamus proper." Walker (1938) suggested that the nucleus may integrate elaborated afferent stimuli, sensory somatic and visceral, projecting them to the cerebral cortex not as sensory modalities but as sensory concepts. The interpretation of the findings

in the present patient is in accord with this view that the dorsomedial nucleus is concerned with somatic sensation, and the findings of the electrophysiologists afford support for the thesis.

Prefrontal Leucotomy

A consideration of the results of prefrontal leucotomy performed for intractable pain, and of the connexions of the dorsomedial nucleus with the frontal lobe, suggest an explanation for the dysæsthesiæ in our patient, and also in those cases of the thalamic syndrome in which the lesion is confined or mainly confined to the lateral nucleus. A considerable literature is being produced on the subject of prefrontal leucotomy, in the treatment of intractable pain (Freeman and Watts, 1946*a*, 1946*b*, 1948*b*, 1948*c* ; Falconer, 1948 ; Koskoff *et al.*, 1948 ; and others). When this operation is performed for severe and persistent pain the patient continues to feel the pain, but he either ignores it altogether or relegates it to an unobtrusive corner of consciousness. If questioned he will admit that his pain is still present but it no longer bothers him. The procedure is not followed by any defect of pain perception. The affective reaction to painful stimuli is lost by reason of the operative division of the fibres connecting the dorsomedial nucleus and the frontal cortex, the connexions with areas 9 and 10 being the most important (Freeman, 1948). There is no reason to suppose that other thalamic nuclei are involved in this reaction to prefrontal leucotomy. This attack upon intractable pain is not invariably successful, the pain may once more become the dominant feature of the sufferer's life after an interval of relief. Weiss, speaking at the National Hospital in February 1949 said that as a result of experiences of this type he would in future restrict his employment of the operation to patients with severe pain from malignant disease.

In thalamic lesions with dysæsthesiæ, and certainly in our case, the connexions between the dorsomedial nucleus and the frontal cortex are often intact. This may well be of some significance. We may reasonably postulate that normally pain impulses reaching the lateral (PLV and PMV) nucleus are relayed not only to the post-central gyrus but also to the dorsomedial nucleus, as Head and Holmes thought ; from here they are projected forward to the frontal cortex. The anatomical and physiological findings which have previously been quoted lend some support to this postulate. In the thalamic syndrome the lateral nucleus is either damaged or destroyed, and under these circumstances two mechanisms may be involved. Firstly, where destruction is incomplete, pain impulses may still be transmitted onwards by the lateral nucleus, but the pattern of excitation is disarranged and a disorderly series of impulses reaches the dorsomedial nucleus, frontal lobe and the parietal cortex. This would have been the position in our patient except that the parietal cortex was cut off from the thalamus, only the thalamo-frontal connexions surviving. Secondly, where destruction in the lateral

nucleus is complete the impulses must achieve consciousness in the thalamus, unless there is an alternative route by which they reach the dorsomedial nucleus or sensory cortex. There is no evidence available to suggest that such pathways exist. Here one might invoke the theory of irritation, re-stated by Martin (1945), and suppose that when destruction of the lateral and the dorsomedial nucleus is complete a discharging lesion might result in impulses being propagated along the sensory pathways to the frontal and parietal cortices.

It has been suggested (Koskoff *et al.*, 1948) that in prefrontal leucotomy there is no interruption of specific pain pathways, despite the evidence of thalamic degeneration, and it should be recalled that Spiegel and Wycis considered the clinical improvement seen after destruction of the dorsomedial nucleus to be comparable with that after leucotomy. The preservation of pain sensibility after leucotomy and the success which has attended the unilateral procedure support this suggestion; nor does it appear that partial lesions of the thalamofrontal pathways produce dysæsthesiæ. Koskoff and his collaborators go on to propound a "concept of suffering as distinct from a concept of pain—an engram of suffering must include the frontothalamic association pathways." They conclude that prefrontal leucotomy becomes "surgery for the relief of suffering rather than surgery for the relief of pain." Faced with the same difficulties Freeman and Watts (1948*b*) define pain as "bodily and mental suffering," the latter being relieved by leucotomy. The fact that leucotomy for pain may fail permanently to achieve its object indicates that the affective element in pain perception, the "mental suffering," is not exclusively appreciated in the frontal lobes. Whether or not there are specific pain pathways running between the thalamus and the frontal lobes it seems unquestionable that impulses associated with pain must pass this way. These impulses may undergo some modification in their passage through the thalamus (Walker, 1938). In our patient this pathway was the only remaining route to the cortex for pain impulses; it seems reasonable to suggest that the dysæsthesiæ may have reached consciousness in the frontal lobe.

But even if these premises be true why should the use of the pathways discussed above result in the appearance of dysæsthesiæ? The key to this problem must lie in a knowledge of the functions of the lateral nucleus. Riddoch (1938), in writing of synapses along the sensory pathways in general, stated the belief that these junctions were sites not only of the relaying of impulses but also of their integration. Lhermitte and Cornil (1929) have stressed the possible role of the lateral nucleus as a modulator of sensory impulses. Presumably the picture envisaged is one of alteration and modification of the rhythm and rate of neuronal discharges. If this conception be true one can regard the dorsomedial nucleus in our case as being bereft of the normal inflow of sensory impulses, receiving in their place a disorderly unmodified stream of impulses from the surviving neurones in the lateral nucleus. One might

expect the result of the arrival of such a pattern of impulses in the frontal lobe to be a disordered sensation of the type described. The work of Adrian (1941), however, does not suggest that sensory impulses are modified in this way. Recording the arrival of sensory impulses at the cortex of experimental animals he found little alteration in the signals on their journey from the periphery, though there were "additional signals from the thalamus which were much more variable." In contrast with these theories which invoke a qualitative change in nerve impulses is that of Le Gros Clark (1947). Hyperpathia and dysæsthesiæ may follow a lesion of the sensory pathways at any point from peripheral nerve to thalamus (Symonds, 1931; Riddoch, 1938). Weddell *et al.* (1948) have brought forward a tentative explanation of the occurrence of dysæsthesiæ in lesions of peripheral nerves on the basis of changes in the pattern of cutaneous innervation. In considering the extension of this theory to explain the production of central pain and hyperpathia in lesions at other levels, they remark the presence of delayed appreciation of painful and thermal stimuli recorded by Kendall (1939) in patients with lesions of the spinal and bulbar sensory pathways. The similarity of this phenomenon to the delay seen in peripheral lesions is apparent. Walker (1938) comments on the presence of delayed sensory appreciation in thalamic lesions. Delayed appreciation of deep pressure pain was present from the outset in our patient. Delayed appreciation of pin-prick, and to a lesser degree of thermal stimuli, was also noted, but this did not appear until the terminal stages of his illness; there was no delay on the normal side at this time. Le Gros Clark's theory is the logical outcome of the observations of Weddell and his collaborators. He remarks that the exaggerated response which occurs in thalamic lesions is probably due "to the partial interruption of pain impulses arriving at the thalamus and thus to a disturbance of the normal pattern of excitation in the higher centres of the brain. This interpretation of the phenomenon of 'thalamic pain' can also be applied to the similar sensory disturbances which may follow lesions partially interrupting spinothalamic pathways in the spinal cord and brainstem." This theory is particularly apposite in those cases in which the lateral nucleus is incompletely destroyed, and so it might be applied to the present patient. The arrival of a highly abnormal pattern of excitation in the frontal lobes, a region preoccupied with the affective response to pain, might be expected to result in the catastrophic, poorly localized sensory experiences which have been related. There are, however, instances of thalamic lesions where the destruction of the organ is so extensive that it is difficult to envisage the passage of any impulses through the thalamus to higher centres. This fact makes it hard to deny that thalamic dysæsthesiæ may indeed be appreciated in the thalamus itself; nevertheless it may be that under these circumstances other mechanisms are involved, such as irritation and the induction of impulses in neighbouring and surviving pathways, whereby an abnormal wave of excitation is propagated to higher centres.

Defective insulation of nerve fibres might play a part in mechanisms of this type.

If the thesis propounded be true the dysæsthesiæ in our patient should have been abolished by prefrontal leucotomy. Freeman and Watts (1946*a*) report two patients in whom the operation had been performed for thalamic pain. In the first case no assessment of the result of the operation was possible owing to the early death of the patient. The second patient had a presumed thalamic lesion, light stroking of the skin causing painful sensations. Pre-operatively there was little sensory loss, and afterwards there was no change in the sensory status, but it now became possible to repeat sensory tests which previously aroused "so much distress that one application met with long and reverberating pain." A third patient reported by the same workers (1948*b*) showed a happier outcome; after operation the application of ice to the affected upper limb produced only brief dysæsthesiæ. The results in the two latter cases would appear to indicate that in them pain impulses were passing beyond the thalamus to the frontal lobes. Preservation of the parietal connexions in these patients may explain the fact that complete relief was not obtained in either case.

Conclusion

There is a certain artificiality about discussions which attempt to localize the various factors which make up the total appreciation of pain. Bishop (1946) writes that "the sensory process presumably involves a considerable amount of cortex and thalamus and possibly of lower centres, and the remainder of crude sense following injury or removal of one region should be looked upon as involving a defect in the normal sensory response, rather than as isolating the focal representation of that sense."

The part of the frontal lobes in the reaction to pain has already been discussed. The place of the parietal cortex in the appreciation of pain has long been under examination. Riddoch (1938) concluded that the sensory (parietal) cortex "is concerned with pain, as with all forms of sensation, but in less degree, and chiefly in respect of its limited discriminative aspects." Many instances have now been recorded of pain occurring in both stationary and progressive lesions of the sensory cortex (Davison and Schick, 1935; Ajuriaguerra, 1937; Michelsen, 1943; and others). Whatever objections may be raised as to the validity of these cases, and also to the occasional occurrence of pain on electrical stimulation of the sensory cortex (Penfield and Boldrey, 1937), the reports of Gutierrez-Mahoney (1944) and Horrax (1946) are convincing in demonstrating that the sensory cortex plays a part in the whole appreciation of pain. Gutierrez-Mahoney succeeded in relieving a patient with painful phantom fingers of the right hand by post-central corticectomy with removal of the corresponding cortical areas, previously defined by electrical stimulation. Horrax had less happy results with a similar operation, the relief of pain being only temporary; but in two cases of

cerebral tumour with central pain the results of post-central corticectomy were much better, one patient being partially and the other completely relieved from pain. In the second case removal of a frontal glioma was followed by pain in the right upper limb. Electrical stimulation of the apposite area in the post-central cortex reproduced the pain; this area was removed with complete relief. Ritchie Russell (1945) has written of the dysæsthesiæ which may follow injuries of the sensory cortex from gunshot wounds; these are similar in every way to those caused by lesions of the sensory pathways at lower levels, but spontaneous pain is very rarely encountered.

These reports suggest that the parietal cortex is concerned with all the aspects of pain appreciation, though mainly with the discriminative side, and the implications with regard to the role of the thalamus are apparent. Prefrontal leucotomy may fail to relieve pain because the remaining parietal cortex is capable of a total reaction to painful stimuli. Further, in any instance of a thalamic lesion in which onward transmission of pain impulses is preserved the parietal cortex should be associated with their appreciation. To obtain full relief from dysæsthesiæ in these circumstances both prefrontal leucotomy and post-central corticectomy would be required. The findings in the present patient suggest that intact thalamo-parietal pathways are essential if thalamic dysæsthesiæ are to have a full hold on consciousness. The thalamus itself stands between the frontal and parietal cortices, receiving and transmitting sensory impulses along its system of double connexions with the two areas. It is hard to deny that appreciation of some forms of sensation may not occur at this level, but such a belief is becoming increasingly difficult to hold. The evidence in favour of bilateral cortical sensory representation has already been discussed. The results of double stimulation in patients with nervous disease underlines the effect of one stimulus upon another under physiological conditions. The complex bilateral nature of the sensory apparatus is further disclosed by the work of Scarff (1948), who showed that unilateral prefrontal leucotomy may relieve ipsilateral, contralateral or bilateral pain.

In 1938 Riddoch wrote "pain is a biological reaction of the individual as a whole," and he went on to consider the part played by personality and physical constitution in the response to pain. The knowledge which has been gained in the past decade enables us to begin to see the anatomical and physiological basis of the reaction of the individual to pain. Pain is indeed a biological reaction of the individual as a whole, and in that reaction the whole brain plays a part.

It is a pleasure to thank Dr. W. Russell Brain for his valuable suggestions and also for permission to publish his patient's case. Professors Dorothy Russell and W. E. Le Gros Clark have lent their aid in the interpretation of the pathological and anatomical features, and to them my thanks are due.

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LEGENDS FOR PLATE

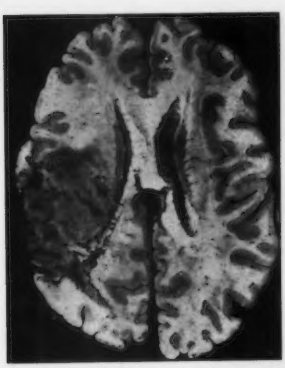
FIG. 1.—Horizontal section of the brain made 5·5 cm. below the vertex. To show the extent of the tumour.

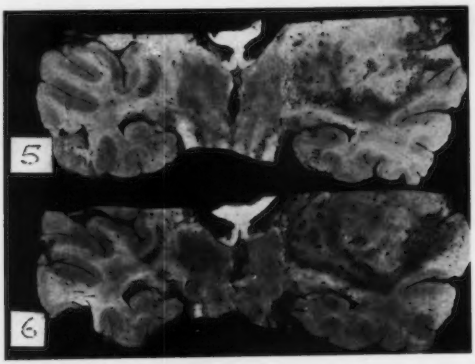
FIG. 2.—Coronal sections of the brain. Fig. 2 (5)—Section at the level of the lateral geniculate bodies. FIG. 2 (6)—Section through the hind-end of the lateral geniculate bodies. To show the relationship of the tumour to the thalamus.

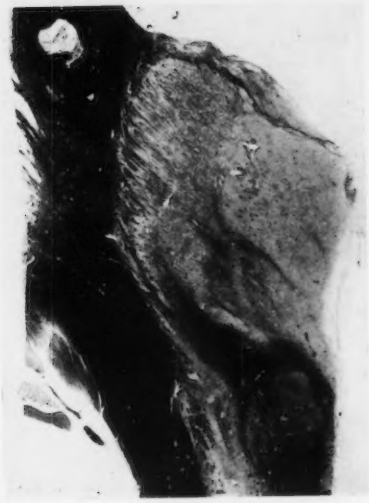
FIG. 3.—Right and left thalami. Section passes through the oral part of the posteromedial ventral, posterolateral ventral and centromedian nuclei. To show the configuration of the nuclei. Loyez' myelin stain. × 2·9.

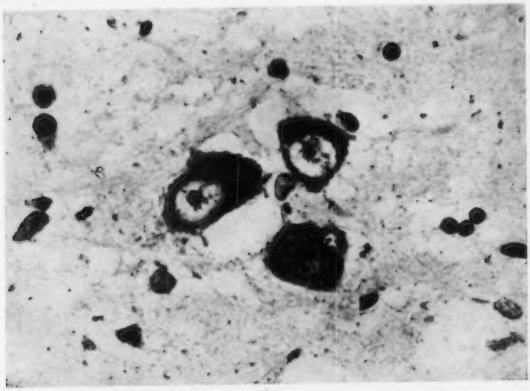
FIG. 4.—Posteromedial ventral nucleus of right thalamus. To show preserved neurones. Nissl stain. × 510.

PLATE XX









To illustrate article by R. A. Henson.

DELAYED WITHDRAWAL REFLEX AND PERCEPTION OF PAIN: STUDIES IN A CASE OF SYPHILITIC MENINGOMYELITIS AND TABES WITH EXTENSOR PLANTAR RESPONSES OF A TYPE NOT PREVIOUSLY DESCRIBED

BY

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RECENT physiological studies to be later referred to have shown a double component in the electromyographic records of extensor plantar responses. This double response appears to be due to the reception of two consecutive nociceptor stimuli, carried respectively by the so-called fast and slow pain fibre components.

The patient reported in this paper showed this double response, the delayed pain perception being associated with a powerful delayed withdrawal reflex of his paralysed legs. The time factors have been electrically recorded and the movements analysed by cinema films and kymographs. The significance of these findings is discussed.

CLINICAL COURSE

In 1910 G. B., then aged 17 years, contracted a purulent penile discharge, diagnosed no doubt correctly as gonorrhœal, for which he received apparently successful treatment. No signs of a chancre were ever detected, but in the following year he noticed a dropping of his right foot which slapped upon the ground as he walked, and soon after he became liable to be incontinent of fæces without warning.

In 1911 he was therefore admitted to the London Hospital where he was found to have a mild spastic paraplegia with extensor plantar responses. No sensory loss could be found but the left pupil was larger than the right and the W.R. was positive in both blood and C.S.F., the latter showing a lymphocytosis. He was treated with mercury, iodides and salvarsan and was improved on discharge. He married and his wife bore him a son, who is still alive and well, and later she had a miscarriage.

In 1916 he joined the Army as C.3 on account of the persistent weakness of his right foot, and was invalided in the following year on account of his incapacity for long marches.

The patient noticed no noteworthy change for nearly ten years, when in 1926 his legs especially the right began to weaken again, and in the

following year he experienced difficulty with his balance in the dark, his feet began to feel numb, and he again had some urgency in defæcation with occasional incontinence. Micturition was unaffected but he began to suffer lightning pains in the legs especially in cold weather.

In 1927 on readmission to hospital he was thin and sallow, with irregular pupils reacting more sluggishly to light than on convergence, and showing slight bilateral ptosis. The mild paraplegia was still present with extensor plantar responses but no longer any spasticity. The right calf was hypotonic, the knee-jerk very feeble and the ankle-jerks absent. The gait was ataxic. Sensory changes were now present in the form of impaired postural sense in the legs, and Rombergism, some impairment to pain and temperature sense as high as the thighs, and to light touch in the feet. Blood W.R. + +. C.S.F. 66 lymphocytes, considerable excess of protein and strongly positive W.R.

1928 : Was readmitted to hospital and given eight malarial rigors after which the condition again ceased to progress until 1933 when his ataxia and lightning pains became worse, and he developed discomfort on taking food and had a hæmatemesis which was the cause of his readmission. A barium meal indicated chronic gastritis but revealed no ulcer.

During the next nine years the condition showed a remarkably slow but steady progression as the infection, but unfortunately not its effects, burnt itself out. The lightning pains became slowly worse in the legs, and occasionally also affected the ulnar side of the hands and arms. By 1940 the C.S.F. was reported as normal in all respects.

In 1942 while in hospital under the care of Dr. Russell Brain, a delay in appreciation of pain was noted for the first time. The patient had begun to have flexor spasms of the legs, beginning with a burning pain in the toes, lasting about five seconds, and more liable to occur when sitting for any length of time. In the following year he reported the absence of bladder sensibility, but had no difficulty in initiating the act of micturition. To avoid incontinence he passed urine regularly every two hours by day and slept with a bottle in his bed at night. He had severe constipation and the occasional fæcal incontinence continued.

By 1945 his postural sensation was so diminished that he had to look at his legs to see whether he was sitting cross legged or not. Lightning pains had now spread to involve the upper abdominal segments.

The flexor spasms gradually became more painful and severe. At first they came on after sitting for half an hour, but gradually began to appear soon after sitting down and continued to recur with violence until he had to get up and walk about, when they ceased at once. The force of the spasms was remarkable, often moving or upsetting a light table at which he was sitting. They were worse when he was in bed and also in hot weather, but never occurred in either leg on standing or walking.

During 1946 a rapid deterioration occurred in both the degree of weakness and ataxia and he was readmitted under Dr. George Riddoch. The pupils were now of fully Argyll Robertson type, and there was considerable over-reaction of the frontales. The arms were normal in power but sensation was impaired to pin and wool along the ulnar border of both hands and forearms, with similar sensory loss over a cuirass area on the chest. The legs were hypotonic, with frequent flexor spasms and showed weakness of dorsiflexion of both feet and of flexion of the right leg. The knee and ankle jerks were absent. The plantar responses were extensor, and the field whence they could be elicited now extended up to the groins. The focus of lowest threshold remained in the lateral aspect of the sole of the foot, and the reflex response itself included a full flexion of the leg. Vibration sense was lost up to the right groin and left knee, postural sense was absent at the ankles and deep pressure pain absent in the calves.

In the cerebrospinal fluid the only traces of the old infection were a Lange colloidal gold curve of 1122110000, a protein content of 20 mg. per cent, no cells, W.R. negative. The lumbar puncture itself produced two interesting ill-effects, firstly the lightning pains were very much increased especially over the left abdomen, and were almost continuous for several days. Secondly the bladder sphincters went into severe spasm, necessitating repeated catheterization. This became increasingly difficult, the last attempt needing an experienced surgeon, when the catheter was tied in for a further three days.

Two years later the legs had become completely atonic, moderate power of extension was preserved but flexion was very weak in the left leg, and he could scarcely draw the right foot up the bed when lying on his back. By keeping his knees braced back with slight genu recurvatum, he could still shuffle along with his sticks. Catheterization to estimate the residual urine led to retention for four days with a distended and very hypotonic bladder. The thoracic aorta was seen to be slightly widened on screening.

Clinical Methods of Study

The time relations of the two modes of response were studied by means of an electric chronometer built on the induction coil principle, which recorded time intervals up to four seconds with a needle traversing a dial calibrated in tenths of a second. The mechanism was started by the observer who pressed a button at the instant the foot was pricked by a pin or stroked by the tip of a Yale key.

The patient, who was insensitive to fast or so-called "first pain," stopped a recording needle by pressing a button the moment he felt the delayed pain.

His reaction time was measured on the same machine, which had indeed been built for that particular purpose.

Cinematograph films were used to illustrate the double nature of the reflexes produced and for these the moment of feeling the delayed pain was marked by the patient lifting his hands.

Only from the distal part of either foot was the production of the extensor plantar response at all constantly seen in its two clearly separate component parts. The focus of election was on the sole 2 cm. proximal to the base of the middle toe.

A sharp steel pin-prick was used in most of the pain timing tests as brevity of stimulus was desirable for accurate timing. A very quick stroking movement with the relatively smooth tip of a Yale key was even more effective as a stimulus of delayed pathological pain and the correspondingly delayed second phase of the plantar response.

Results

(1) A sensation was felt as the pin penetrated the skin, and was discerned as sharp, and punctate, and he could always distinguish it from the glass head of the pin. There was, however, no sensation of a painful prick. Immediately on receipt of this stimulus there was a rapid and isolated dorsiflexion of the hallux.

(2) A delayed abnormal pain was next felt after a variable interval of from 0·5 second to 3·5 seconds, with an average of 2·2 seconds over 52 recordings. The quality of the pain was more like that of cramp than anything else that the patient had previously experienced. It was very painful and this fact put a definite limit upon the number of readings that could be taken at any one session. His reaction time averaged 0·4 second.

(3) A delayed flexor withdrawal reflex in either leg occurred synchronously with the onset of pathological pain.

The extensor plantar response therefore clearly occurred in two parts. The first was an immediate dorsiflexion of the hallux through a considerable angle which lasted just over a second. The toe had returned to its neutral position before the more massive delayed withdrawal reflex had begun.

In this second phase dorsiflexion of the hallux took no conspicuous part. The hip, knee and ankle all flexed together in a slow movement up the bed until the heel was only 6 inches from the buttocks.

The power of this flexor movement was remarkable. In response to the most vigorous encouragement, the patient could only draw his right heel a few inches up the bed, and the examiner's index finger on the dorsum of the foot could easily keep the whole limb immobile in extension. In response to an adequate stimulus for the delayed pain, flexion of the right leg was so powerful that it could not be prevented by the full power of the right arm of a colleague of average physique. Cinematograph recordings of the movements, both unhindered and against the above resistance, were made by the writer and all the above phenomena were carefully checked by projecting the films by slow motion. Isolated

dorsiflexion of either hallux could be invariably obtained by stroking the sole gently with the pad of a finger.

The accompanying kymographic recordings show the two component parts of the Babinski reflex and their respective connexion with fast and slowly conducted sensation.

In this case the fast sensation appears to have been mediated by receptors responding to touch heavy enough just to deform the skin, such as a slight stroke with a finger pad or the smooth tip of a Yale key.

A response to such a slight stimulus is common in severe cases of paraplegia and the adequate stimulus may be extremely light as in this case. Such very light stimuli were insufficient to cause the delayed pain.

A more powerful stroke with a finger pad or finger nail, or heavier pressure with the Yale key, would still produce the first component, but after this had subsided the delayed response would appear synchronously with the delayed pain.

Fig. 1 shows two consecutive responses F_1 and F_2 to rapid but very light strokes S_1 and S_2. No delayed pathological pain was excited and no corresponding delayed withdrawal reflex appeared.

The third stimulus S_3 was made with greater pressure on the Yale key and although the first component was similar in all respects, the

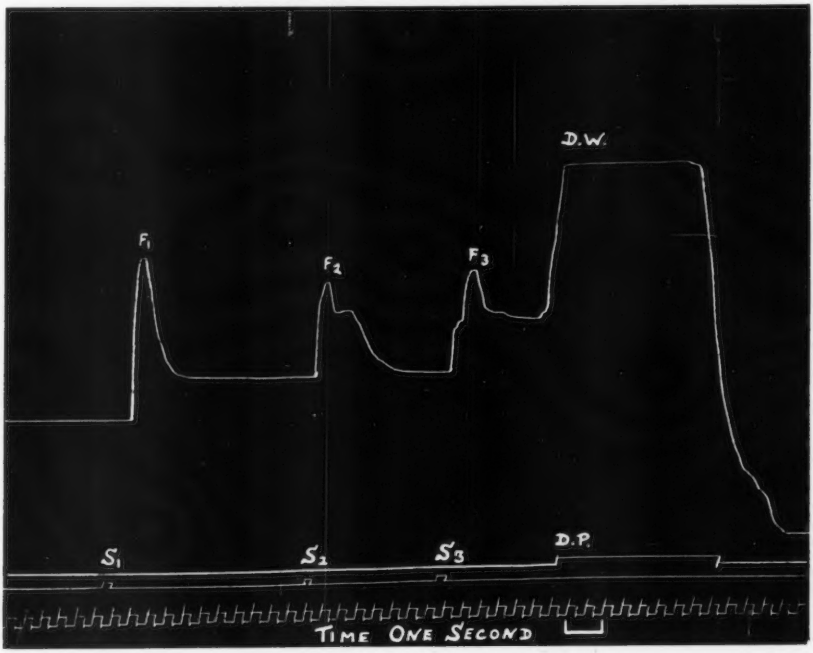

FIG. 1 (*see* under fig. 2).

patient felt the delayed " slow pain " and depressed the bell button at D.P., keeping it down throughout the 4½ seconds that it lasted.

At the same moment that he felt the pain the delayed withdrawal reflex occurred and subsided again at the moment the pain ceased.

The patient's measured reaction time averaged 0·4 second and in this tracing the delayed reflex precedes the pain marker by almost exactly this amount.

Sixteen similar records of this double plantar response were taken consecutively and showed no material variation in any of the time factors. No delay reads more than three seconds and none below 2·5 seconds.

Fig. 2 shows the double response without the preceding subliminal reflexes recorded in fig. 1.

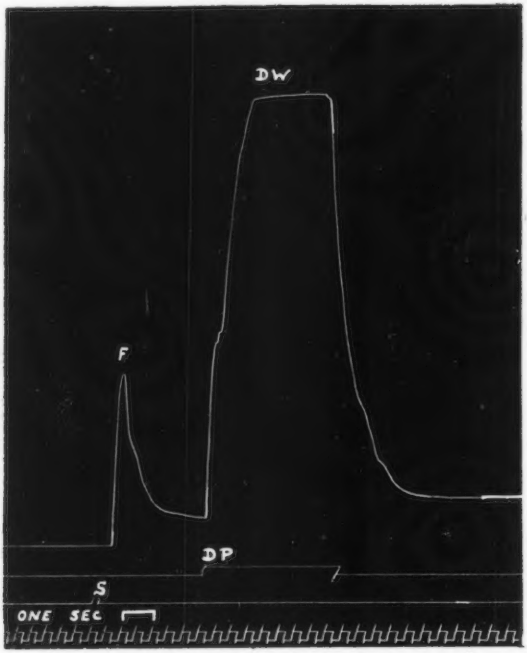

FIG. 2.

Key to figures.

Figs. 1 *and* 2.—Reading from left to right, markers in order from above downwards. F = First component in Babinski reflex due to " fast " sensory conduction of touch. D.W. = Delayed withdrawal reflex, the second component of the Babinski reflex activated only by delayed pain carried in slow conducting fibres. Delayed pain line marking onset of pain at upstroke D.P. S_1 and S_2 on line below —light stimuli adequate only for responses F_1 and F_2. S_3 heavier stimulating stroke producing D.P. and D.W. after three seconds' delay. Time marker in half and quarter seconds.

The time marker was a clockwork driven electric impulse mechanism recording in half and quarter second strokes of the electromagnet.

The kymograph pen was connected by linen thread over a pulley to the tip of the right hallux and was mounted on a light vertical rod sliding in precision bearings, thereby ensuring that all timing analysis was accurate and readable without correction. Any vertical line dropped to the time marker gives the true reading from the upstroke of S in quarter seconds.

The stimulus marker was connected to a piece of thin wire strapped transversely to the sole of the right foot at the junction of the posterior and middle thirds. The quick stroke of the smooth brass key was begun just over the wire which lay on a thin piece of strapping to prevent any electric impulse stimulating the patient.

Painful Spontaneous Flexor Spasms

These phenomena usually start with a severe burning sensation in the sole of the right foot, followed almost immediately by a flexor spasm of withdrawal. The quality of the pain he describes as being similar to, but not identical with, that felt as a result of stimulation of the sole but is rather less severe. Never does the patient experience a marked delay, such as a second or more, between the pain and the flexion.

The frequency of these painful spasms is very variable, hardly a day passes without one, but they never occur except when he is sitting or lying, unless he sustains a painful stimulus such as stubbing his toes or shin, or by dropping something heavy on to his feet, in which case a flexion reflex may bring him to the ground. Gowers reported a case of similar falls from sudden pain (1898).

A mosquito bite on his leg or foot has on several occasions precipitated a shower of flexor spasms which has lasted up to two days, and occurring every few minutes, with peaks of up to every ten seconds. Repeated stimuli from the clinical investigations were also liable to increase the flexor spasms for a few hours.

The lightning pains from which the patient greatly suffers are of the usual type, worse in cold weather but unaffected merely by damp.

Discussion

Recent work on pain has thrown much light on the phenomena described above.

The double pain response was first described by Rosenbach in 1884, and he attributed the delayed pain in tabes (Remak, 1874) to the normal second pain which was later studied and timed by Pochin (1938).

The physiological basis of these findings was classified by the work of Gasser and Erlanger (1927) who described the A.B. and C fibres with their different sizes and proportional conduction rates, and the further studies of the slow conducting C fibres by Clark, Hughes and Gasser (1935) who suggested that these thin unmyelinated fibres conduct the

second pain response at about 1 metre per second. Bishop and Heinbecker (1935) brought further evidence that the C fibres carry pain. Lewis and Pochin (1938*a* and *b*) further analysed the double pain responses. More recently it has been customary to refer to the B fibres as δ fibres of group A, conducting " first pain " at about 25 m/sec., Zotterman (1939). No mention of a double element in the Babinski reflex has been found in the literature until the recently published paper by Kugelberg (1948), following the work of Lloyd (1943) on cats, which showed two separate elements in the flexion reflex, the first from the fastest sensory fibres and the second from the relatively slower δ fibres of group A. Kugelberg demonstrated A and C fibre components of the Babinski reflex by electromyography in tibialis anterior and extensor hallucis longus in patients with spinal cord lesions. The second response attained its maximum more slowly and took longer to subside, with correspondingly slower movements of the leg, foot or toe. He also found a prolonged stimulus such as a scratching movement more effective than a pin-prick. He suggested that this slow rise and fall might be due to a difference in the spinal mechanisms of the reflexes, but might also be explained by the differences in the afferent arc, a more prolonged after-discharge due to a wider spread of the range of conduction velocities in the fibres mediating the second response.

Pochin (1938) found only a small variation in delay, 1·5 to 2·0 seconds for second pain in normals, and 1·5 to 1·9 seconds in tabetics. In the latter the delay averaged 1·7 seconds in the toes, 1·5 seconds at the ankles and 1·1 seconds at the knees. Kugelberg's patients showed a wider range, 1·3 to 2·3 seconds in ten different cases both with heat as a stimulus, and when stroking with a needle. He found the latency longer for tall persons than for short, and found variations in the same subject of up to $\frac{1}{2}$ second according to the intensity of the stimulus.

In the subject of the present paper, the variation was still greater, 0·5 to 3·5 seconds, and no relationship could be detected with variations in the strength of stimulus, nor any from a possible refractory state immediately after a flexion reflex. Greater delays than this, not mentioned by Pochin, have been described. Gowers reports seven seconds in a personal case (loc. cit. p. 453) and cites Eulenberg as describing a fifteen seconds delay in pain perception. One of Kendall's (1939) patients had a delay of four seconds to thermal stimuli.

By a simple calculation of the latencies at the toe (1·5 seconds), and at the knee (1·05 seconds), Kugelberg estimated the conduction rate of the C fibres concerned to be about 1 metre per second in a case of paraplegia in flexion.

The double response in the present patient was only obtainable on the foot, so no direct calculation was made. With a similar reaction time and average delay of 2·2 seconds the speed of slow nociceptive conduction in the present patient is clearly in the C group of $\frac{1}{2}$ to 2 metres per second.

The mechanism underlying these great variations in delay is not known, and indeed there may be several contributory factors.

A cardinal feature of delayed pain is its prolonged action. In all experiments upon the timing of this pain, it has been the delay between the stimulus and its first appreciation that has been measured, and I have found no records elsewhere of its actual duration, the longest period it lasted in the present study was 11·2 seconds. On this occasion the stimulus was a quick stroke with a smooth Yale key and the delay was 1·4 seconds. Abnormal painful impulses were therefore still reaching consciousness over 12½ seconds after a stimulus which would have caused only momentary discomfort to a normal foot. The patient showed no trace of hyperæsthesia nor any soreness of his feet, and it seems reasonable to conclude that this prolonged sensation of abnormal pain was due largely, if not entirely, to slow conduction.

Now the C wave of conduction is a very protracted one in the normal neurogram and it is suggested that in tabes and possibly other conditions, not only are fast δ fibres destroyed, but the faster elements of the C group are impaired selectively as compared with the slower ones conducting at half a metre per second. There is reason to think that there are some very small fibres with conduction rates considerably slower than this.

The existence of such very slow fibres, all faster ones having been destroyed in the tabetic process, would adequately explain the cases of extreme delay cited by Gowers, and the protracted shower of pain producing impulses which lasted for 12·6 seconds in this patient.

Variations of delay in a patient can similarly be explained by inconstancy of conduction of any given strength of impulse in the more damaged but rather faster elements of the C group of fibres.

In addition to the possibility of such delay by conduction through a decrement, delay could also occur at synapses. It is hard to see, however, how such great delays as above described could occur at the few synapses crossed in the passage of pain to consciousness.

Types of Positive (Extensor) Plantar Responses

It is frequently doubtful whether a plantar response is abnormal or not. Associated contraction of the hamstrings as stressed by Walshe in 1914, although a reliable minimal response in advanced cases, has proved disappointing in the doubtful cases where confirmation is so badly needed.

The purest and most reliable response is generally regarded as an isolated dorsiflexion of the hallux which should be obtained by grading the stimuli till only this occurs. Withdrawal of the foot is frequently voluntary, but an isolated upward toe movement is probably never so.

Fanning of the toes is again unusual in mild cases and therefore of little help. It is certainly unreliable if occurring alone. The opposite toe sometimes moves but with no apparent constancy of direction.

The speed of the movement of the hallux has been regarded as helpful, the more reliable responses appearing to be the slower ones. The case here presented and the work of Kugelberg suggests that this speed of response is more dependent upon the conduction speed of the noxious stimulus than upon the site and severity of the pyramidal lesion.

A quick up and down movement of the toe is more usually found in mild cases, and the very slow or delayed movement is usually associated with more severe pyramidal lesions with one important exception, and that is in conditions where there has been blocking of the fast δ fibres of group A, and preservation of the slower ones, combined with a pyramidal lesion.

Such a combination can occur in neurosyphilis. Peripheral nerve lesions in tabes, first described by Westphal and later by Pierret (1880), cited by Gowers (1899), were regarded by the latter as common. The pyramidal element arises from associated myelitis or general paresis.

With regard to threshold for the A and C types of plantar response, in the present case a light touch such as with a finger pad would produce a quick " A type " dorsiflexion of the toe as described above (fig. 1).

Kugelberg also found a lower threshold for the " A fibre flexion reflex " from mechanical stimulation of the sole. Using heat as a stimulus he found the C response had the lower threshold. Precisely similar results were obtained in the present patient, and an adequate thermal stimulus in the form of a smooth container of water at 160° F. (71° C.) placed against the sole for one second produced a delayed withdrawal reflex but no quick " A fibre " toe movement.

The properties of the C response are probably bound up closely with the quality of second pain, the function of which is more impelling in its nocifensor reaction than the bright first pain with its quick warning which can be ignored until the very unpleasant and even nauseating quality of the more slowly conducted pain compels physiological retreat. The pathological basis of this second pain is still unsettled, and indeed the recent work of Weddell *et al.* (1948) throws the whole problem still deeper into the melting pot. It appears that this noxious pain can be produced in several ways, peripherally through thinning of the pain-subserving network (Weddell, loc. cit.), and centrally as in the cases described by Kendall (loc. cit.) with lesions in the ponto-bulbar and lower cervical region, and in the thalamic syndrome itself. In the present case a biopsy by Weddell from the dorsum of the foot whence noxious pain could be elicited, showed a normally dense pain fibre network and cutaneous end-organs, and in addition a new type of nerve ending not as yet described. In the present case the lesion lies in a site between those of Weddell and Kendall though whether in the large peripheral nerves, roots or cord it is not possible to say. The patient unquestionably has a severe cord lesion from his original meningomyelitis and such a site could also be responsible for the delay, as will be discussed below.

Lewis and Pochin (1938*a*) showed clear evidence that the slow conduc-

tion was in the peripheral nerves only, and drew diagrams illustrating that they had been unable to find " second pain " within an area whose boundaries were equidistant from the spinal cord. Within this area the latency below 0·5 second was too small to detect clinically.

Kugelberg (1948) came to a similar conclusion by recording the moment of feeling first or second pain at the same time as taking an electromyograph tracing of the reflex response. When the reaction time of 0·3 second was substracted, the pain was found to be synchronous with the motor discharge excited from the local spinal reflex centre, whereas the pain had had to travel to the thalamus. The timing was the same for fast and slow pain indicating that these two sets of impulses travel equally fast in the spinal cord. The distance concerned is approximately 50 cm. and were conduction continued at the C rate of $\frac{1}{2}$ to 2 m.p.s., the additional delay of $\frac{1}{4}$ to 1 second should have been observed by Kendall and Pochin.

Kendall (1939) postulated separate pathways in the cord for both fast and slow pain, and indeed the delay in his cases caused by pontobulbar and cervical cord lesions, does not seem explicable on any other basis. There is no necessity, however, for Kendall's implied assumption (p. 258) that these functionally separate pathways conduct at materially different speeds.

The accompanying diagram (fig. 3) which incorporates some of Kugelberg's measurements and time records, and which is also in full agreement with the findings of Lewis and Pochin (1938*a*) shows evidence that the slow conduction ends at, or very near, the point of entry into the cord at the S_1–L_4 segments.

Any lesion above this point may destroy the fibre pathways carrying fast pain, but leave those conducting the impulses brought to the lumbar cord by the slow C fibres of the peripheral nerves.

If the opposite occurs and the impulses from the C system are destroyed then the absence of slow pain may be missed, or, more likely, the patient is found to have impared sensation to pain, still feeling the prick, but not getting such an unpleasant (C conducted) sensation as from the opposite side.

Whatever the precise mechanism, the disproportionate violence of the reaction to slow pain is well seen both in the quality of the pain felt and in the primitive motor response of withdrawal, far transcending the maximal voluntary power of the paralysed victim.

It is reasonable to consider briefly the value or benefit derived from the possession of a slow pain fibre system when the organism has already been warned by the fast pain.

The very brevity of fast pain may be a source of danger. In flight or fight, a brief flash of pain, however extreme, might be ignored if replaced too soon by the other impelling stimuli crowding into a harassed or excited sensorium.

Survival is too important to depend on the vagaries of after-discharge,

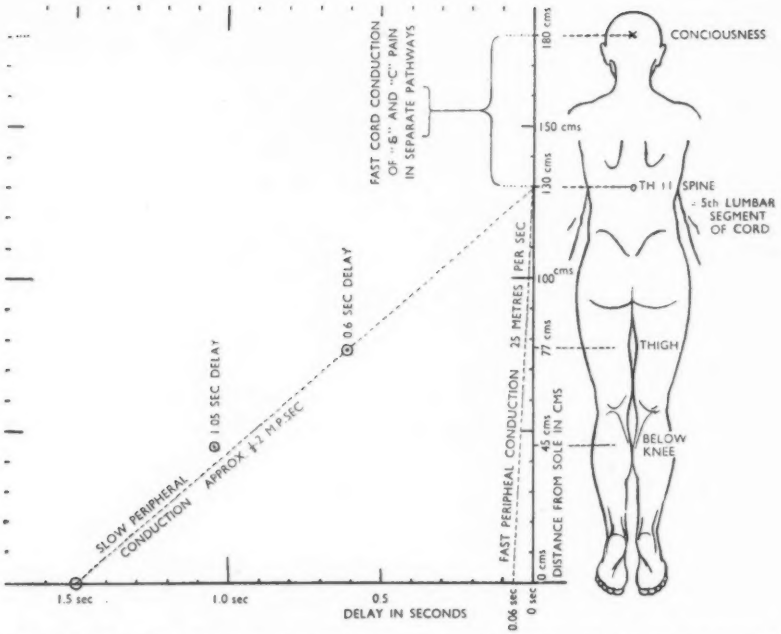

FIG. 3.—Graphic diagram illustrating proportional delay of slowly conducted "second pain," and illustrating the probable sites of fast and slow conduction as described in the text.

and it seems reasonable to suggest that a continuous flow of impelling but protective sensations has been ensured by means of slow conduction in a separate group of fibres with a wide range of velocities.

None of the evidence here discussed, nor any from the present case, seems to refute the widely held conception that the arrival of fast pain modifies the affective results of the slower pain.

The suggestion that the inhibition of the more unpleasant qualities takes place distally to the thalamus (Riddoch and Critchley, 1937, and Riddoch, 1938) seems unnecessary, provided that the existence of a double set of fibres in the cord is accepted.

The conception of actual inhibition at any level may be misleading, and it is preferable in many ways to regard abnormal and excessive pain reactions as liable to occur whenever pain-producing impulses reach consciousness in a crude or imperfect form.

As more precise knowledge is acquired it becomes ever less necessary to invoke the functions of inhibition to explain the well-ordered actions of the nervous system in health and disease.

Clinical experience indicates that the distortion of this pattern may occur at many sites and from widely different causes.

On this basis any lesion of the sensory pathway from the skin network described by Weddell (1948) to the level of the thalamus itself may prevent the reception of the fast pain impulses necessary for the normal sensations of pain. Thus as Symonds said, of central pain from clinical reasoning in 1931, " the essential condition for the production of this syndrome at whatever level is a certain degree of incompleteness of the lesion."

States of pathological pain in the face probably work through a similar mechanism but there are considerable technical difficulties in timing delays over such short distances and in such inaccessible sites.

It has been objected that anterolateral sections have abolished all forms of pain, but this only suggests that the double central pathways run close together. They may even intermingle histologically but minute physiological differences in their metabolism could account for the interference of the one and not the other by the factors of nutrition, pressure and œdema, all of which may play their part in affections of the spinal cord.

Indeed the baffling variety of symptoms in spinal tumours alone, often ill-fitted to purely anatomical arrangements of tracts, and the remarkable selectivity of functional loss in modalities known to run in the same tracts, have long since convinced neurologists that these metabolic factors of nutrition, pressure and œdema are more important than mere localization of any given fibre.

Other conditions will also produce the markedly delayed withdrawal reflex. I have recently studied a bedridden case of Friedreich's ataxia under Dr. William Evans in the London Hospital for the rare combination of this disease with paroxysmal auricular tachycardia and 2 : 1 block.

In this patient no A component in the reflex could be obtained at all, but a massive withdrawal reflex, more powerful than his best voluntary efforts, occurred after a delay which varied between the close limits of 1·5 to 1·75 seconds timed over ten readings for each foot.

A further case of tabes with an additional pyramidal disorder has been studied and this also showed a very quick " A fibre " type of Babinski toe response followed by a delay of $1\frac{1}{2}$ to 4 seconds after which an extremely unpleasant pain was felt and was accompanied by a withdrawal reflex.

He was too ill with bronchopneumonia for more extensive study, but these three cases suggest that these phenomena, so simple to explain on physiological grounds, are in fact not so very uncommon.

I have sought this delayed reflex in subacute combined degeneration as here pyramidal lesions occur in combination with early destruction of the largest fibres (Greenfield and Carmichael, 1935). So far this has not been found, presumably because although the touch, position, and vibration carrying fibres in the large diameter 90-100 meters a second class are characteristically damaged, sufficient δ fibres survive to give a quick pain and early type of Babinski reflex.

I wish to express my thanks to Dr. Russell Brain and those other members of the staff of the London Hospital, both past and present, under whose care this patient has rested during his numerous admissions since 1911, and to Dr. Walshe for much helpful criticism in the final preparation of this paper.

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THE CROSS-SECTIONAL AREA OF PERIPHERAL NERVE TRUNKS OCCUPIED BY THE FIBRES REPRESENTING INDIVIDUAL MUSCULAR AND CUTANEOUS BRANCHES[1]

BY

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FOLLOWING the suture of a severed nerve or an injury which disrupts the endoneurial tubes regenerating axons from the proximal stump must compete for the available endoneurial tubes in the distal stump since there is no mechanism which ensures that each axon will selectively re-enter its corresponding endoneurial tube and thereby fully reconstitute the fibre pattern. In this process the chances of re-establishing old connexions are favourable only when the injury is sustained or the suture is executed at a level at which there is some degree of localization of fibres representing the individual branches (*see* Sunderland, *Brain*, 1945, for a discussion of this subject). At levels where no such localization exists and the branch fibres are intermingled and widely distributed over the funiculi comprising the nerve trunk, the number of fibres for each individual branch has an important bearing on the effectiveness of regeneration since, if the fibres of a branch are numerous, there is more chance of some of their regenerating axons reaching corresponding endoneurial tubes. A contributing factor in this regard is the branching of the axon sprouts which occurs with the commencement of regeneration in the proximal stump. When, on the other hand, the fibres to a branch are few in number, their chances of establishing correct continuity when competing for endoneurial tubes will be correspondingly reduced. The competition for endoneurial tubes becomes particularly acute at levels where the nerve is composed of a single funiculus which contains all the fibres of all the branches. Such an arrangement is not uncommon in the ulnar nerve in the vicinity of the elbow, in the radial nerve in the spiral groove and in the lateral popliteal nerve in the distal third of the thigh.

When, therefore, suture is performed at levels where each, or most, of the constituent funiculi contains fibres from most, or all, of the branches so that there is no, or very little, fibre localization in the nerve trunk the number of fibres for each individual branch becomes a factor influencing the restoration of the fibre pattern. This information would be of value in understanding the variations in the extent and quality of recovery following repair but the task of counting the total number of fibres representing

[1]This work was assisted by a grant from the National Health and Medical Research Council of Australia.

each of the muscular and cutaneous branches in a peripheral nerve would be formidable. Furthermore it is the percentage distribution of the different branch fibres in the individual funiculi in the nerve which is the significant factor, but there is as yet no method of ascertaining this information. The cross-sectional area of the funiculi devoted to individual branches (within the branch itself and within the nerve trunk before fibre-mixing results from funicular anastomoses) may, however, be accepted as an indication of the number of, and the proportionate area occupied by, its constituent fibres in the nerve trunk and of the influence of this factor on regeneration. The cross-sectional area of the nerve trunk occupied by each branch of the radial, median, ulnar and sciatic nerves has accordingly been measured with this object in view. In this connexion it should be noted that the cross-sectional area of a funiculus must be regarded as an approximate, and not an accurate, measure of its fibre-content since the relationship is affected by several factors such as the degree of myelination of the nerve fibres, the amount of intrafunicular connective tissues and the amount of shrinkage occurring during preparation.

Preliminary figures for radial, median and ulnar nerves have already been published (Sunderland, 1945) but the values given in this paper are based on a much larger series of specimens.

It is emphasized that several factors affect the entry of regenerating axons into funiculi. This paper, however, is confined to a consideration of only one of these, namely the factor which influences the entry of axons into corresponding endoneurial tubes in the funiculi thereby affecting the restoration of the fibre pattern.

Material and Methods

The observations were made on 12 specimens of the ulnar nerve, 11 specimens of the radial (below the origin of the posterior cutaneous nerve of the forearm) and 10 specimens each of the median and sciatic nerves. Each nerve and its branches were carefully and fully dissected. Each branch was sectioned at its origin to determine its funicular pattern and cross-sectional area. The blocks of tissue were prepared, sectioned and stained under comparable conditions. They were fixed in formalin, embedded in paraffin, sectioned at 15 μ and stained with hæmatoxylin and eosin. Material rendered unsatisfactory by shrinkage was discarded and a new series obtained. The sections were enlarged on a microprojector to a constant magnification and drawn. The cross-sectional areas of the funiculus or funiculi representing individual branches (excluding the perineurium) were then measured with a planimeter. The cross-sectional areas of the various branches were totalled and the cross-sectional area of each branch was then expressed as a percentage of this.

The areas given in the tables were obtained at the point where the branches left the trunk. In some specimens it was difficult to ascertain accurately whether or not some articular branches contributed fibres to

adjacent muscles close to or through which they passed (e.g. to the extensor digitorum longus from the articular branches to the knee-joint from the anterior tibial nerve). However, in the instances in which this may have occurred the contribution could not have been great. Some difficulty was also experienced in differentiating arterial branches; where uncertainty existed no values are given. In the case of the median and ulnar nerves the few specimens in which values were obtained suggested that the cross-sectional area devoted to arterial branches above the wrist would not exceed 2 per cent. In the tables the section "Terminal Sensory" for the median, ulnar and anterior tibial nerves includes the cutaneous, articular and arterial branches to the hand and foot which were not differentiated in the dissections.

Results

The proportion of the total cross-sectional area of the funiculi of the nerve trunk which is occupied by the fibres comprising the various branches of each of the four peripheral nerves is given in the tables. Reference to these values will suggest the possible influence of this factor on the nature, course, extent and usefulness of regeneration.

Features requiring special emphasis are:

(1) The relative cross-sectional area occupied by the fibres representing each branch naturally depends on the level at which the analysis is made. Thus the fibres comprising the branches of the median and ulnar nerves in the hand occupy a greater area in the nerve in the forearm than in the upper arm where fibres for branches to the forearm muscles are included.

For this reason the medial and lateral popliteal divisions of the sciatic nerve have been considered separately in the popliteal fossa and in the buttock (Tables IV to VII). In addition, values have been given for the sciatic nerve in the buttock by considering the nerve as a single trunk without any subdivision into its component popliteal sections (Table VIII).

(2) The variation in the percentage incidence of the cutaneous fibres in different specimens is attributable to observed variations in the extent of the peripheral distribution of the cutaneous branches. This variation influences the readings for the other branches in the same nerve.

(3) There is a high percentage of sensory fibres in the radial and lateral popliteal nerves. In the case of the radial nerve there is, within and below the spiral groove of the humerus, a quandrantic localization of the branches within the nerve which is sufficient (providing correct axial alignment is maintained during suture) to reduce the wasteful regeneration occasioned by the growth of muscular and cutaneous axons into cutaneous and muscular endoneurial tubes respectively. At the lateral humeral epicondyle the superficial radial fibres are contained in a separate bundle group which occupies the anterior portion of the nerve. In order to exclude any possible wasteful cross-shunting of regenerating axons when the nerve is repaired at this level the cutaneous section should be isolated and sutured separately if this is practicable.

At a level approximately 3 to 4 cm. above the head of the fibula, most of the funiculi of the lateral popliteal nerve (excluding those representing the sural communicating branch and lateral cutaneous nerve of the calf) contain representatives of all branches given off below the knee. Since, above that level, the fibres of the distal branches are intermingled and widely scattered over the funiculi comprising the nerve trunk, the chances of regenerating sensory axons excluding motor axons in the competition for endoneurial tubes becomes considerable. This may be one of the reasons why suture of the lateral popliteal nerve in the thigh is often followed by such poor motor recovery. Such wasteful regeneration will be accentuated when the suture is performed above the level of origin of the sural communicating and lateral cutaneous of the calf branches since the established practice is to suture the entire nerve trunk, thereby permitting the fibres of these cutaneous branches to compete for motor endoneurial tubes of the muscular branches.

The fibres of the sural communicating nerve and lateral cutaneous nerve of the calf remain confined, however, within a separate bundle group which can be identified and isolated for some considerable distance up to the thigh. In Table IV these cutaneous fibres have been included with the remaining branches of the lateral popliteal nerve. If, however, a cross-sectional analysis is made below their origin, or by excluding them at the higher level, the following values are obtained :

	Below the origin of the sural communicating and lateral cutaneous of the calf	*Above the origin of the sural communicating and lateral cutaneous of the calf*
Total muscular	45	34
Total sensory (cutaneous and articular)	53	64
Total arterial	2	2

A comparison of the two sets of values will serve to illustrate the advantage to be gained, following nerve division, by isolating the bundle groups containing the sural communicating and lateral cutaneous fibres and suturing them separately ; by this method the regenerating cutaneous fibres of these two branches will be prevented from competing for the endoneurial tubes in the remainder of the trunk as occurs when trunk suture alone is performed.

(4) (*a*) In general, the nerve fibres representing branches to large muscles occupied greater cross-sectional areas in the funiculi than those representing small muscles but not always proportionately so since other factors, such as the role of the muscle in executing finely adjusted movements in more complicated movement patterns, are operating. For this reason the proximal muscles of the limbs, which are larger than those of the distal parts, have a greater representation in the funiculi.

(*b*) In general, branches leave the peripheral nerve trunks in the vicinity of the elbow, hip and knee and in the hand and foot.

(*c*) It has been shown (Sunderland, 1945) that the funicular intercommunications which occur in the intraneural plexuses are of such a nature that the dispersal and intermingling of fibres which they occasion is gradual and, at any one level, produces only a minor degree of intraneural shift of fibres. Thus, despite the changing plexiform character of the funicular pattern, fibres from branches pursue a relatively localized course in the nerve for variable, though often considerable, distances. The scattering of fibres occurs gradually and only as the intercommunications are repeated at successive levels so that widespread intermingling and dispersal of fibres is achieved only after they have ascended considerable distances along the nerve. For these reasons the longer the course of a branch within a nerve, that is the longer the nerve and the more distal the site of entry of the branch, the greater the diffusion and the intermingling of its fibres at proximal levels. When, however, the bundles of a branch which has a very high origin commence to anastomose, they do so with bundles which have acquired fibres from most, if not all, of the distal branches. As a result the fibres of such proximal branches are rapidly mixed with those from several sources, but since their intraneural course before reaching the axilla or buttock is too short to permit extensive scattering, they remain relatively discretely localized, though in combination.

(*d*) Proximal muscles often combine as prime movers in executing movements and for this reason the reinnervation of one member of the group by fibres originally supplying another does not greatly disturb the pattern. Consequently for the purposes of assessing the restoration of the fibre pattern during recovery, these muscles may be regarded as forming a functional unit. The two heads of gastrocnemius and soleus, the hamstring group, the peronei and the extensors of the wrist are examples in point. On the other hand the muscles controlling the digits function as independent but well-integrated and co-ordinated systems in every movement, combining to give that delicacy, refinement and precision of action which, in the case of the hand, is the basis of manual dexterity. In these complex and finely adjusted movement patterns each muscle has a specific role to play. Consequently any disturbance of the fibre pattern during the regeneration of fibres to these muscles seriously limits the restoration of function.

Correlating these four observations it follows that conditions are more favourable for recovery in the proximal than in the distal muscles after repair in the proximal part of the limb because (i) their fibres occupy a greater cross-sectional area at the site of suture, (ii) they are better localized at proximal levels than the fibres destined for structures further distally, and (iii) the common action often shared by the proximal muscles assists in the restoration of function. At levels in the forearm and leg where no localization obtains recovery will, other things being

equal, favour structures innervated by branches whose fibres occupy the greater cross-sectional area of the nerve. At the wrist and ankle, where the fibres of the terminal branches are partly or sharply localized in the nerve trunk, such a localization will, providing correct funicular relations can be maintained during repair, compensate in part for any disadvantage pertaining to a branch because of the small number of its component fibres. However, regardless of the degree of localization obtaining, the more regenerating fibres there are corresponding to a particular structure the greater the chances of recovery in that structure though the quality of the recovery will depend on the number of the fibres reaching their destination and the extent to which they reconstitute the pattern.

Summary

Values have been obtained for the cross-sectional areas of peripheral nerve trunks occupied by the fibres representing individual muscular and cutaneous branches of the radial, median, ulnar and sciatic nerves.

The significance of this data has been discussed in relation to the reconstitution of the fibre-pattern during the regeneration of axons following an injury disrupting the endoneurial tubes and after suture of the nerve.

An explanation is provided to account for the observation that, after repair in the proximal part of the limb, the extent and quality of the recovery in the proximal muscles usually exceeds that in the distal.

REFERENCE

SUNDERLAND, S. (1945) *Brain*, **68**, 243.

TABLE I.—THE RADIAL NERVE

The Percentage Cross-sectional Area of the Radial Nerve Occupied by the Fibres of Individual Branches

							Individual branches of the posterior interosseus nerve							
Specimen	*S.R.*	*B.*	*B.R.*	*E.C.R.L.*	*E.C.R.B.*	*P.I.*	*S.*	*E.C.U. E.D.Q. E.D.C.*	*E.I.P.*	*A.P.L.*	*E.P.B.*	*E.P.L.*	*Total muscular*	*Total sensory*
1	25	—	5	11	8	51	10	20	5	3	5	8	75	25
2	29	—	6	12	8	45	14	12	4	8	3	4	71	29
3	34	—	7	11	8	40	7	7	2	8	6	10	66	34
4	37	3	6	10	6	38	3	16	2	5	4	8	63	37
5	23	2	6	7	10	52							77	23
6	33	—	4	8	6	49							67	33
7	25	1	4	5	8	57							75	25
8	30	2	3	10	7	48							70	30
9	31	5	6	7	7	44							69	31
10	26	3	12	7	8	44							74	26
11	25	3	10	8	7	47							75	25
Mean (per cent)	29	2	6	9	7	47							71	29

S.R. = Superficial radial ; B. = Brachialis ; B.R. = Brachioradialis ; E.C.R.L. = Extensor carpi radialis longus ; E.C.R.B. = Extensor carpi radialis brevis ; P.I. = Posterior interosseous ; S. = Supinator ; E.C.U. = Extensor carpi ulnaris ; E.D.Q. = Extensor digiti quinti ; E.D.C. = Extensor digitorum communis ; E.I.P. = Extensor indicis proprius ; A.P.L. = Abductor pollicis longus ; E.P.B. = Extensor pollicis brevis ; E.P.L. = Extensor pollicis longus.

TABLE II.—THE MEDIAN NERVE

The Percentage Cross-sectional Area of the Median Nerve Occupied by the Fibres of Individual Branches

				Total medial epicondylar muscle		*Individual branches of the anterior interosseous nerve*								
Specimen	*P.T.*	*F.C.R.*	*F.D.S.*	*mass*	*A.I.N.*	*F.D.S.*	*F.D.P.*	*F.P.L.*	*P.Q.*	*P.C.*	*Terminal muscular*	*Terminal sensory*	*Total muscular*	*Total sensory*
1	7	4	6	17	9	1	3	3	2	1	5	68	31	69
2	5	5	12	22	11		6	2	3	2	3	62	36	64
3	5	6	9	20	13						2	65	35	65
4	6	4	10	20	10						4	66	34	66
5	7	6	7	20	14						5	61	39	61
6	4	3	6	13	10						3	74	26	74
7	7	5	6	18	12						6	64	36	64
8	5	4	5	14	9						6	71	29	71
9	6	4	8	18	13					2	3	64	34	66
10	5	4	6	15	13					2	1	69	29	71
Mean (per cent)	6	4	7	17	11					2	4	66	33	67

P.T. = Pronator teres ; F.C.R. = Flexor carpi radialis ; F.D.S. = Flexor digitorum sublimis ; A.I.N. = Anterior interosseous nerve ; F.D.P. = Flexor digitorum profundus ; F.P.L. = Flexor pollicis longus ; P.Q. = Pronator quadratus ; P.C. = Palmar cutaneous ; Total medial epicondylar muscle mass = the sum of P.T., F.C.R. and F.D.S.

TABLE III.—THE ULNAR NERVE

The Percentage Cross-sectional Area of the Ulnar Nerve Occupied by the Fibres of Individual Branches

Specimen	*F.C.U.*	*F.D.P.*	*P.C.*	*P.C.H.*	*Terminal sensory (superficial division)*	*Terminal muscular (deep division)*	*Total muscular*	*Total sensory*
1	13	7	1	11	32	36	56	44
2	7	7	6	23	29	28	42	58
3	13	7	—	15	39	26	46	54
4	12	6	2	14	40	26	44	56
5	13	2	—	13	39	33	48	52
6	7	3	—	15	43	32	42	58
7	10	3	1	26	33	27	40	60
8	14	8	—	18	33	27	49	51
9	8	6	—	17	39	30	44	56
10	13	5	1	24	34	23	41	59
11	14	9	—	21	34	22	45	55
12	9	9	1	16	33	32	50	50
Mean (per cent)	11	6	2	18	35	28	46	54

F.C.U. = Flexor carpi ulnaris ; F.D.P. = Flexor digitorum profundus ; P.C. = Palmar cutaneous ; P.C.H. = Posterior cutaneous of the hand.

TABLE IV.—THE LATERAL POPLITEAL DIVISION OF THE SCIATIC NERVE IN THE POPLITEAL FOSSA ABOVE THE ORIGIN OF THE SURAL COMMUNICATING AND LATERAL CUTANEOUS OF THE CALF BRANCHES

The Percentage Cross-sectional Area of the Lateral Popliteal Division of the Sciatic Nerve in the Popliteal Fossa Occupied by the Fibres of Individual Branches

	Muscular							*Cutaneous*								
Specimen	*P.L.*	*P.B.*	*Total peronei*	*T.A.*	*E.D.L.*	*E.H.L.*	*E.D.B.*	*S.C.*	*L.C. of calf*	*Cut. of M.C.*	*Term. sensory of anterior tibial*	*Arterial*	*Articular*	*Total muscular*	*Total sensory (cutaneous and articular)*	*Total arterial*
1	11	3	14	5	4	2	1	20	7	32	8	2	5	26	72	2
2	10	5	15	10	7	3	1	5	11	24	17	3	4	36	61	3
3	10	7	17	11	4	3	1	9	18	22	10	1	4	36	63	1
4	– 20 –		20	9	6	2	1	10	14	18	12	1	7	38	61	1
5	9	6	15	10	5	3	2	7	8	32	12		6	35	65	
6	8	5	13	7	4	4	2	8	10	29	10	3	10	30	67	3
7	12	5	17	10	5	2	2	7	6	41	7		3	36	64	
8	14	5	19	7	3	3	2	9	17	27	8		5	34	66	
9	10	4	14	9	5	3	2	20	10	19	7	3	8	33	64	3
10	9	6	15	10	9	5		4	15	21	11		10	39	61	
Mean (per cent)	11	5	16	9	5	3	1	10	12	26	10	2	6	34	64	2

P.L. = Peroneus longus ; P.B. = Peroneus brevis ; Total peronei = the sum of P.L. and P.B. ; T.A. = Tibialis anterior ; E.D.L. = Extensor digitorum longus ; E.H.L. = Extensor hallucis longus ; E.D.B. = Extensor digitorum brevis ; S.C. = Sural communicating ; L.C. of calf = Lateral cutaneous of calf ; Cut. of M.C. = Cutaneous of musculocutaneous nerve.

TABLE V.—THE LATERAL POPLITEAL DIVISION OF THE SCIATIC NERVE IN THE GLUTEAL REGION

The Percentage Cross-sectional Area of the Lateral Popliteal Nerve in the Gluteal Region Occupied by the Fibres of Individual Branches

	Muscular								*Cutaneous*								
Specimen	*B.F.*	*P.L.*	*P.B.*	*Total peronei*	*T.A.*	*E.D.L.*	*E.H.L.*	*E.D.B.*	*S.C.*	*L.C. of calf*	*Cut. of M.C.*	*Term. sens. A.T.*	*Arterial*	*Articular*	*Total muscular*	*Total sensory (cutaneous and articular)*	*Total arterial*
1	8	10	3	13	5	3	2	1	18	6	30	7	2	5	32	66	2
2	4	9	4	13	9	6	3	1	5	11	24	17	3	4	36	61	3
3	6	9	6	15	10	4	3	1	9	17	21	9	1	4	39	60	1
4	5	– 19 –		19	9	5	2	1	10	14	16	11	1	7	41	58	1
5	8	8	6	14	9	5	2	2	7	7	30	11		5	40	60	
6	8	8	4	12	7	4	4	2	7	9	26	9	3	9	37	60	3
7	8	11	4	15	9	4	2	2	6	6	39	6		3	40	60	
8	7	13	4	17	6	3	3	2	8	16	26	7		5	38	62	
9	5	9	4	13	9	5	3	1	19	9	19	7	2	8	36	62	2
10	9	8	5	13	9	8	5		3	14	20	10		9	44	56	
Mean (per cent)	7	9	5	14	8	5	3	1	9	11	25	9	2	6	38	60	2

B.F. = Biceps femoris ; Term. sens. A.T. = Terminal section of the anterior tibial nerve (cutaneous, articular and arterial). For the identification key to the remaining branches *see* Table IV.

TABLE VI.—THE MEDIAL POPLITEAL DIVISION OF THE SCIATIC NERVE IN THE POPLITEAL FOSSA

The Percentage Cross-sectional Area of the Medial Popliteal Nerve in the Popliteal Fossa Occupied by the Fibres of Individual Branches

	Muscular								*Cutaneous*								
Specimen	*M.G.*	*L.G.*	*S.*	*Total muscular to calf*	*P.*	*T.P.*	*F.D.L.*	*F.H.L.*	*Sural*	*Med. calc.*	*Arterial*	*Articular*	*Plantars*	*Total muscular*	*Total sensory (cutaneous and articular)*	*Total plantars*	*Total arterial*
1	6	6	14	26	6	3	3	2	4	8	0·3*	4	44	40	16	44	0·3
2	6	3	9	18	3	3	2	2	6	3	0·4*	1	62	28	10	62	0·4
3	4	4	7	15	5	3	2	2	6	10	1	5	51	27	21	51	1
4	5	3	7	15	4	5	4	3	8	4	1	5	51	31	17	51	1
5	6	7	11	24	5	3	2	2	6	6	0·4*	5	47	36	17	47	0·4
6	5	4	9	18	4	7	1	2	4	9		8	47	32	21	47	
7	6	3	12	21	2	2	2	2	5	4	1	1	60	29	10	60	1
8	8	6	9	23	3	4	1	2	7	12	0·3*	3	45	33	22	45	0·3
9	8	4	13	25	4	3	3	3	4	10	1	4	43	38	18	43	1
10	4	5	7	16	8	2	2	2	9	5	0·5	3	53	30	17	53	0·5
Mean (per cent)	6	4	10	20	4	4	2	2	6	7	1	4	50	32	17	50	1

M.G. = Medial head of gastrocnemius ; L.G. = Lateral head of gastrocnemius ; S. = Soleus ; P. = Popliteus ; T.P. = Tibialis posterior ; F.D.L. = Flexor digitorum longus ; F.H.L. = Flexor hallucis longus ; Med. calc. = Medial calcaneal cutaneous ; Total muscular to calf = the sum of M.G., L.G. and S.

*Omitted from analysis.

Notices of Recent Publications

The Treatment of Acute Compound Injuries of the Spinal Cord Due to Missiles. By D. D. Matson. Pp. 64. Oxford: Blackwell Scientific Publications Ltd.

The author's intention in writing this monograph has been to make available the general consensus of opinion among neurosurgeons in the United States Army concerning missile wounds of the spinal cord. This has been achieved lucidly and concisely and the result will be of interest to those concerned in the treatment of civilian spinal injuries as well as those which result from warfare. It is pointed out that in World War I the mortality of missile wounds of the cord was 71·8 per cent with, in the best hands, an operative mortality of 62·2 per cent. In World War II the mortality fell to 15 per cent and the post-operative mortality was 5 to 12 per cent in different series. While no figures are available to indicate a greater incidence of functional recovery after the modern surgical therapy of these wounds it is pointed out that the indications for operation have been extended.

The types of wound are classified and the method by which the cord is injured in each considered and related to prognosis. The pathology of the cord lesion is considered and it is again stressed that compression is the sole factor responsible for neurological disturbance which can be relieved by surgery. The first-aid treatment and investigation of the patients is discussed and the indications for early laminectomy considered in detail. The latter are three, the prevention of local and meningeal infection, the relief of pain, and the removal of extrinsic compression. It is of course in the latter group that the surgeon is often in doubt as to whether or not the neurological disturbance is due to intrinsic cord damage or to compression. The author advises laminectomy here when the picture is one of a partial lesion with evidence of progression or when in the absence of such progression there is radiological evidence of encroachment upon the spinal canal by bone or foreign bodies. In cases in which the lesion is clinically complete operation is advised in cases where X-ray reveals encroachment upon the canal, especially if the missile has not crossed the mid-line. When such a complete lesion is associated with a missile track passing from one side of the mid-line to the other through the spinal canal the prognosis is at its worst.

The technique of the operation and post-operative care are considered and brief reports of illustrative cases from the author's series are added.

Acute Injuries of the Head. By G. F. Rowbotham. Third Edition. 1949. Pp. 480. E. & S. Livingstone.

The third edition of this popular textbook has appeared after an interval of four years. It is slightly larger than the previous one, the number of illustrations has been increased and as in the past the subject is fully considered from the viewpoints of pathology, diagnosis and treatment. Prognosis not only as regards survival but also recovery of function receives due emphasis and the importance of rehabilitation in minimizing disability is indicated. The book is thus of undoubted value to all concerned in the treatment of head injuries and the author's frequent references to the literature makes easily available further information on the various aspects of the subject.

In the section on the pathology of blunt injuries there are numerous excellent illustrations of the various lesions which may occur. The difficult diagnostic problems which may follow such injuries receive detailed consideration and of especial interest is the attempted correlation of abnormal postures and movements with the physiological level of the injury to the motor pathways. It is stressed that inspection holes are indicated in all those cases in which a massive intracranial hæmorrhage may be present—a point of greatest importance since most extradural hæmorrhages—at all events—are probably not associated with any so-called lucid intervals. All aspects of the treatment of blunt head injuries are fully considered, and in this connexion it is of interest to note that the author suggests a number of indications for subtemporal decompression.

The simpler problems of compound depressed fractures and penetrating brain wounds receive shorter space. In dealing with fractures involving the paranasal sinuses the author does not indicate whether or not he considers that exploration of the fracture line with dural repair, if required, is or is not to be done in all cases. The infective complications of

penetrating wounds are fully described. There are chapters dealing with the sequelæ of brain injuries in general and of injuries of particular parts of the nervous system and the pathology and clinical features of cerebral birth trauma are discussed. Post-traumatic epilepsy also receives full consideration.

Among the outstanding features of the book may be mentioned the excellent illustrations —in particular the reproductions of X-ray films; numerous informative statistical tables compiled by the author or obtained from the literature are of great value; and not least there is throughout evident the author's sympathetic attitude to the disabled patient and his unwillingness to dismiss as neurotic symptoms for which no clear explanation can be found.

There is little to criticize here but one wonders if clarity might not have been better achieved by reserving the term concussion—as Trotter did—for disturbance of brain function of essentially transient type, and if the more severe injuries with prolonged unconsciousness might not be better grouped together under the heading of cerebral contusion and lacerations. While it is clear that in such cases the superficial contusions do no more than contribute to the prolonged unconsciousness it is not unlikely that the diffuse, though less marked, pathological changes scattered through the brain are a very important factor in delaying or preventing the return of consciousness. It might be too that in a future edition by a process of crystallization the author might be able to shorten some sections thus preventing such further enlargement of the book as would detract from its value.

Pathology of the Nervous System. By J. HENRY BIGGART. Second Edition. 1949. Pp. 352. With 232 Illustrations and 10 Coloured Plates. Edinburgh: E. & S. Livingstone.

While the second edition of Professor Biggart's textbook is still a lucid and well-illustrated introduction to the subject it may be doubted if the needs of the present-day student of neuropathology or even of the candidate preparing for one of the more testing diplomas of psychological medicine have been adequately met. It may be a matter of opinion as to what should or should not be included in an elementary textbook of this sort, but although much new matter has indeed been added, there are some surprising omissions. For example, no mention has been made of inclusion body encephalitis or of the subacute sclerosing encephalitis of van Bogaert. There is, moreover, a noticeable poverty of reference to experimental neuropathology, an aspect of the subject instructively presented in a recent American textbook.

Students of mental deficiency may justifiably complain that their speciality has also been neglected since the account given of the lipoidoses, birth injuries, cerebral palsies and the commoner malformations is unnecessarily superficial. In the section on cerebral tumours one looks in vain for some reference to the important objections made by Scherer and others to the Bailey and Cushing classification of the gliomas which in this edition still retains its pride of place. Nor is the book very helpful as a source of reference since many of the names of authors whose work is quoted in the text have been omitted from the bibliography given at the end of each chapter.

The reader is left with the impression that what is still in many ways a good introduction to neuropathology would have been made an excellent one had not the author underestimated the student's need of a wider acquaintance with the modern literature.

Psychological Aspects of Clinical Medicine. By STEPHEN BARTON HALL. 1949. Pp. xii + 416. 6 Illustrations. London: H. K. Lewis and Co., Ltd. Price 21s.

This book is based on a course of clinical lectures to final year and postgraduate medical students at Liverpool. More than any other extant text, it pays attention to the clinical psychiatric problems that arise in the practice of a general hospital. The entire arrangement of the book is different from that of a textbook of psychiatry; and the author's interest is devoted almost entirely to the mutual relations between emotional disturbance and bodily illness, the commoner neuroses and disorders of personality, and the psychological aspects of treatment. The considerable significance for the general physician of psychotic manifestations does not, perhaps, meet with sufficient appraisal. Nevertheless to this relatively uncultivated field, the happy hunting ground of the fanatic and the quack, the author brings sound common sense, a lack of bias and dogma, and the application of well-tested clinical methods. It should be read with profit by even those students and medical men who have no special interest in psychological medicine, though some will find it rather long-winded.

Die Angstneurose: Enstehung und Heilung. By W. BITTER. 1948. Pp. 191. Bern: Hans Huber. Swiss Fr. 9.80.

This book might have been called a contribution to comparative psychodynamics. The main attention is given to the theoretical explanations of the origin of anxiety states provided by Freud and by Jung; but other psychodynamic schools, such as that of Adler, are discussed, and mention is made of the views of other clinicians such as Bleuler, Jaspers, Schneider, Schultz, etc. The physiological basis of anxiety states is, however, neglected. A third of the book is taken up with the analysis of two patients, one by a Freudian and the other by a Jungian technique. It is convincingly demonstrated that neither has any great advantage over the other, and that both are so flexible that the clinical findings can be fitted into the schemata they provide. The author believes that some patients are best treated by the Freudian method, some by the Jungian, and that the clinician should be able to distinguish between the two classes of case. To the critic it would appear that if each of the two theories is equally near the truth, it may be because each is equally far. If two mutually incompatible theories provide equally satisfying explanations, neither is satisfactory.

Critical Studies in Neurology. By F. M. R. WALSHE. 1948. Pp. 256. Edinburgh: E. & S. Livingstone. Price 15s.

The author has collected a series of critical reviews published in BRAIN during the past few years. There is also a foreword "on the function of criticism in medicine" and an address on "the integration of medicine."

Diseases of the Nervous System. By F. M. R. WALSHE. Sixth Edition. 1949. Edinburgh: E. & S. Livingstone. Price 17s. 6d.

The edition is no larger than its predecessors, but contains a recasting of the chapter on the pathology and treatment of neurosyphilis. Such other changes have been made as advances in knowledge have called for.

The Structure of Medicine And its Place Among the Sciences. By F. M. R. Walshe. (Harveian Oration before the Royal College of Physicians of London, 1948.) Edinburgh: E. & S. Livingstone. Price 1s. 6d.

The roles and nature of observation and experiment in medicine and those of art and science are discussed in general terms. A case is made for regarding the roots of the scientific method as being found in the mediæval liberal arts of grammar, logic and rhetoric. Finally, a plea is made for a philosophy of medicine as the only remedy for its progressive degradation into a chaos of technologies.

Einfuhrung in Die Neurologie. By OSKAR GAGEL. 1949. Berlin: Springer Verlag. D. Marks 30.

A compendium of applied anatomy and physiology for the clinical neurologist of a kind now appearing in various countries. It would be unkind to reproach the author for not having embodied in his work the advances in knowledge that the past twelve or fifteen years have brought, for he must have been cut off from neurological literature during the greater part of this period. The work is in essence a précis of the views and teaching of Otfried Foerster, and embodies the views of this most distinguished clinician upon such subjects as cortical cytoarchitectonics and their physiological bearings, but perhaps does scant justice to work in other countries.

Thus, Lassek's work on the origin of the pyramidal system, the now manifestly dubious attribution to the Betz cells of this origin, and Lashley and Clark's critique of cortical cytoarchitectonics find no mention.

Nevertheless, it contains a mass of information well ordered and clearly expounded. Thus, it is a good representation of a point of view which held the field before 1939. If read, with these limitations in mind, it will prove of value to the neurological student.

Sir William Gowers: A Biographical Appreciation. By MACDONALD CRITCHLEY. 1949. Pp. 118. London: Wm. Heinemann Medical Books. Price 17s. 6d.

Dr. Critchley has done well to summarize for us the work of this great clinician of the Victorian era, to give him his rightful place amongst the founders of modern neurology, and to salve for us from the fading past something of the striking personality of his subject. Some of Gowers' most distinguished pupils have been among the leaders of neurology in our own time, and from them he has been able to glean those personal reminiscences that are the making of a readable biography.

Nor is the subject of this biography an easy task for the writer, for he lived at a time when uniformity, that hallmark of a disintegrating society, had not blurred the outlines of those men of forceful character in whom the Victorian period was so rich. It is impossible to fit Gowers into the category of those of whom the writers of obituary notices can find nothing better to tell us than that they were never known to say an unkind word of anyone.

To be a house physician to Gowers was to hear quite a number of unkind words, but their stimulating and inspiring fruit may be seen in the number of neurologists of the first rank who learned their rudiments and the rigours of the clinical method at its incomparable best from this astringent teacher. Their names, like Gowers', are written in our literature.

In this chronologically arranged record, Gowers' successive contributions are dealt with, and a full bibliography concludes this little volume.

Every neurological aspirant today strives to acquire an old copy of Gowers' Manual, and to it Dr. Critchley has provided an appropriate companion volume.

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